

20<sup>TH</sup>

# INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 21-22, 2023



20<sup>TH</sup> ULMANN  
20<sup>TH</sup> International Ultmann Chicago Lymphoma Symposium



A photograph of the Chicago skyline at dusk or night, showing the city's skyscrapers reflected in the water in the foreground. The sky is a mix of blue and orange hues.

Historical Perspectives:  
Follicular Lymphoma

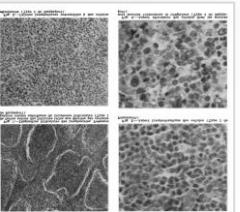
Leo I Gordon, MD



# **Disclosures**

- **Ono Pharmaceuticals: Consultant**
- **BMS: Advisory Board**
- **Kite: Advisory Board**
- **Janssen: DSMB**
- **Zylem, Inc: Co-founder**

## 1925-1938



- **Brill-Symmers Disease:** Brill et al JAMA 1925; Symmers Arch Pathol 1938

## 1979

- **Observation in FL:** Portlock et al Ann Int Med 1979



## 1980-1987

- **4D6 Ab :** Miller et al NEJM 1982
- **1F5 Ab:** Press et al Blood 1987



## 1993-2002



- **Vaccine:** Tao and Levy Nature 1993; Timmerman et al Cancer Res 2002
- **IDEA C2B8 (rituximab):** Maloney Blood 1997; Maloney JCO 1997
- **RIT:** Tositumomab: Kaminski et al NEJM 1993; Ibrutinomab tiuxetan: Witzig et al JCO 1999
- **R-CHOP:** Czuczman et al BLOOD 1997

## 2009-11



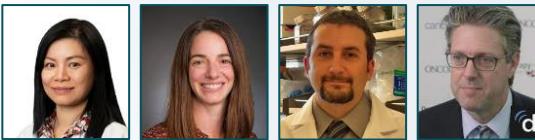
- **FLIPI 2:** Federico et al JCO 2009
- **R Maintenance:** Hochster, H et al JCO 2009 ; Salles et al Lancet 2011

## 2012-15

- **Observation:** Solal-Celigny JCO 2012
- **R vs W&W:** Ardesna et al Lancet Oncol 2014; Kahl et al RESORT JCO 2014
- **No advantage Id vaccine:** Levy et al JCO 2014
- **R<sup>2</sup>:** Fowler et al Lancet Oncology 2014
- **POD 24:** Casulo et al JCO 2015
- **M-7 FLIPI:** Pastore et al Lancet Oncology 2015



## 2021-23



- **CAR T: ELARA:** Fowler et al Nature Medicine 2021; **ZUMA 5:** Jacobson et al Lancet Oncol 2022
- **Bi-Specifics :** Budde et al Lancet Oncol 2022
- **Founder Mutations in FL :** Schroers-Martin et al Cancer Discovery 2023



## 2003-06

- **Observation vs treatment:** Ardesna et al Lancet 2003
- **FLIPI 1:** Solal-Celigny et al BLOOD 2004
- **Molecular Features of FL:** Dave et al NEJM 2004
- **R-CVP vs CVP:** Marcus et al BLOOD 2005
- **R-CHOP vs CHOP:** vanOers et al BLOOD 2006



# Brill-Symmers Disease

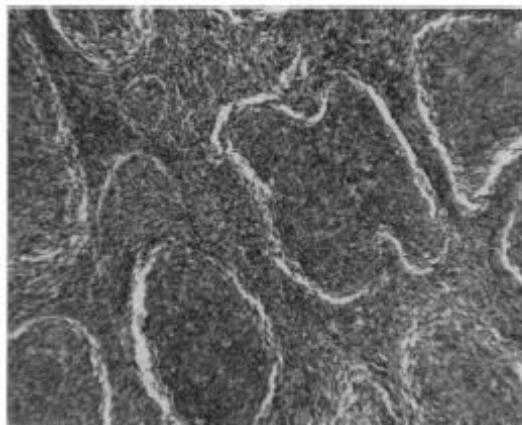


Fig. 1.—Disposition folliculaire des lymphocytes. Présence de failles autour des follicules telles que décrites par certains auteurs comme spécifiques du lymphome folliculaire (Type 1 de Rappaport).

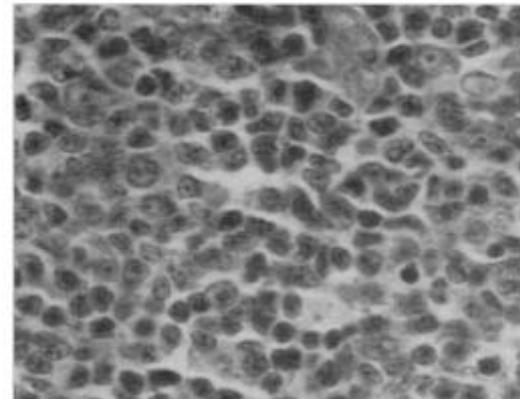


Fig. 2.—Aspect lymphoblastique des cellules (Type 2 de Rappaport).

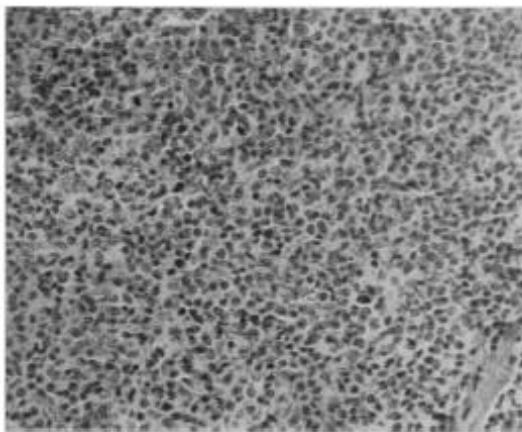


Fig. 3.—Cellules lymphatiques entremêlées à des cellules réticulaires (Type 3 de Rappaport).

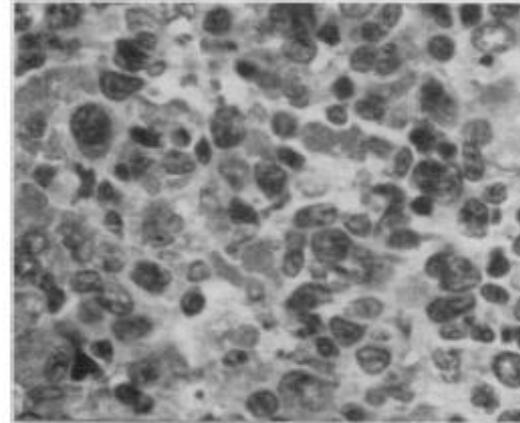


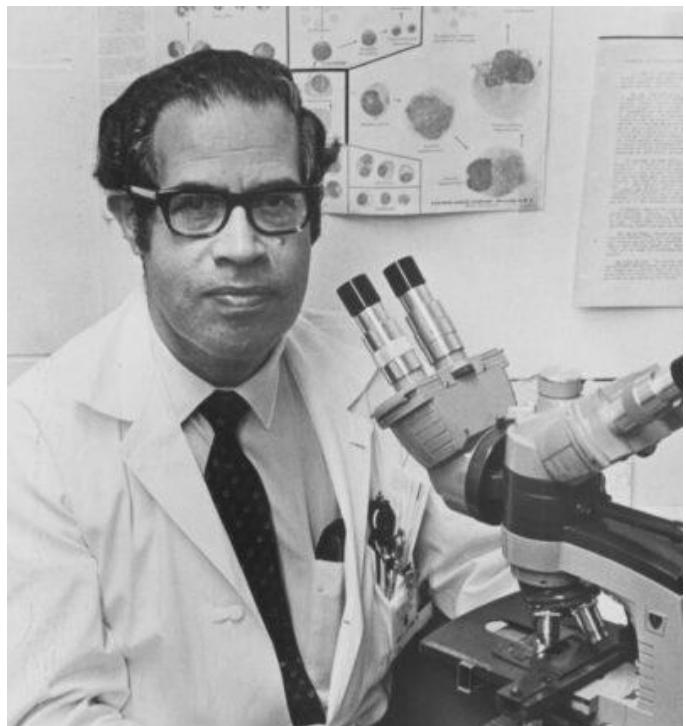
Fig. 4.—Aspect réticulaire des cellules dont les noyaux sont souvent volumineux et irréguliers (Type 4 de Rappaport).

Brill, N.E, Baehr, G and Rosenthal, N. Generalized giant lymph follicle hyperplasia of lymph nodes and spleen. JAMA 1925; 84:668  
Symmers, D. Giant follicular lymphadenopathy with or without splenomegaly. Arch Pathol 1938; 26:603

**The Occurrence of Lymphoma in Patients with  
Long-standing Hyperthyroidism**

*By JOHN E. ULMANN, GEORGE A. HYMAN AND BURTON CALDER*

Blood 1963 Vol 21 No.3:282



**NON-HODGKIN'S LYMPHOMA:  
MANAGEMENT STRATEGIES**

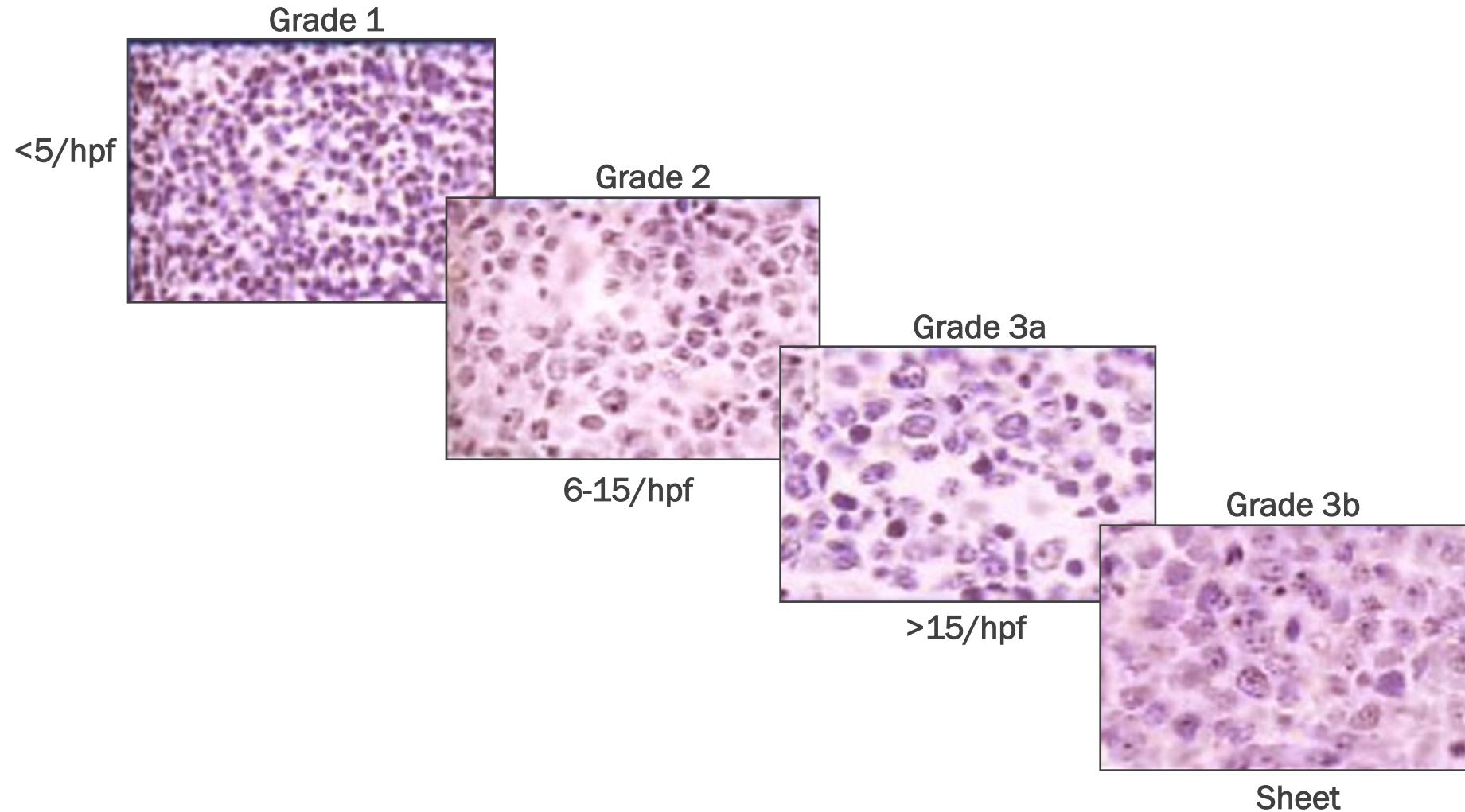
The New England  
Journal of Medicine

University of Chicago  
Chicago, IL 60637

ELLEN R. GAYNOR, M.D.  
JOHN E. ULMANN, M.D.

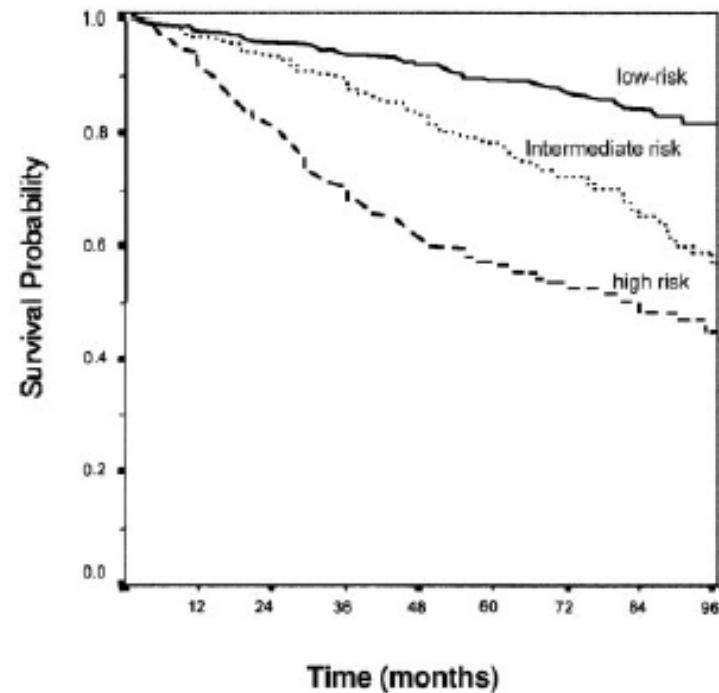
NEJM 1984 311 No.23: 1506

# WHO/REAL Grading For Follicular Lymphoma



# FLIPI 1

Solal-Celigny et al BLOOD 2004



Age < 60 or > 60

Number of Nodal Sites (0-4 vs. >4)

Hemoglobin >12 vs. < 12

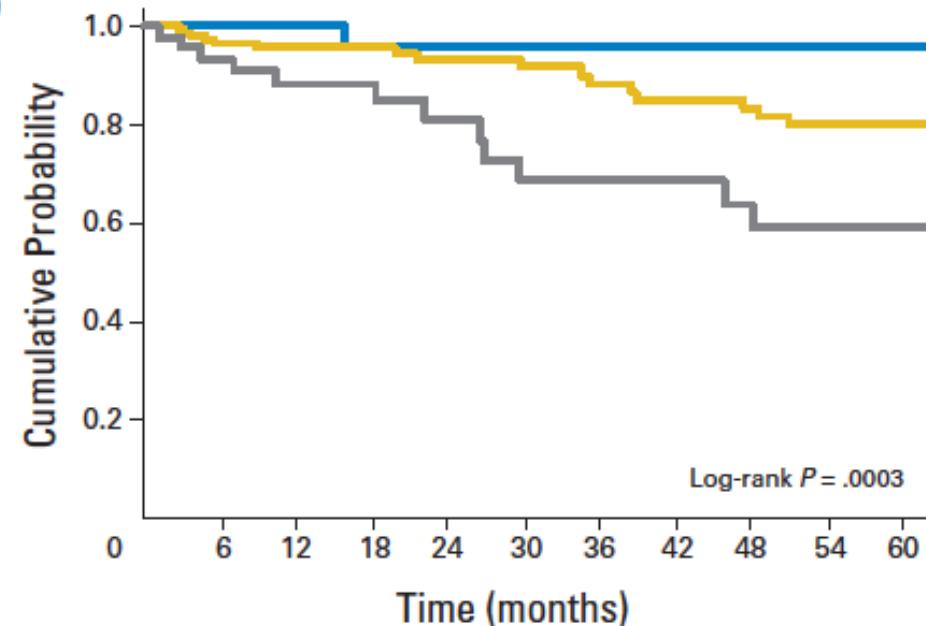
Stage (I, II vs. III, IV)

# FLIPI 2

Federico et al JCO 2009



D



Age < 60 or > 60

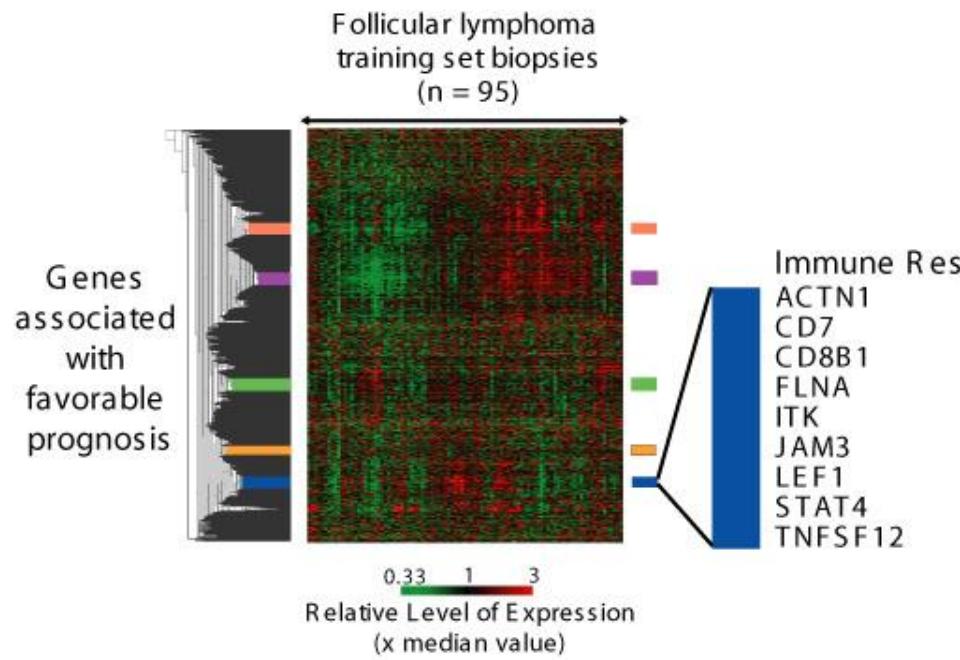
$\beta$ -2 microglobulin

largest node >6 cm

Marrow Involvement

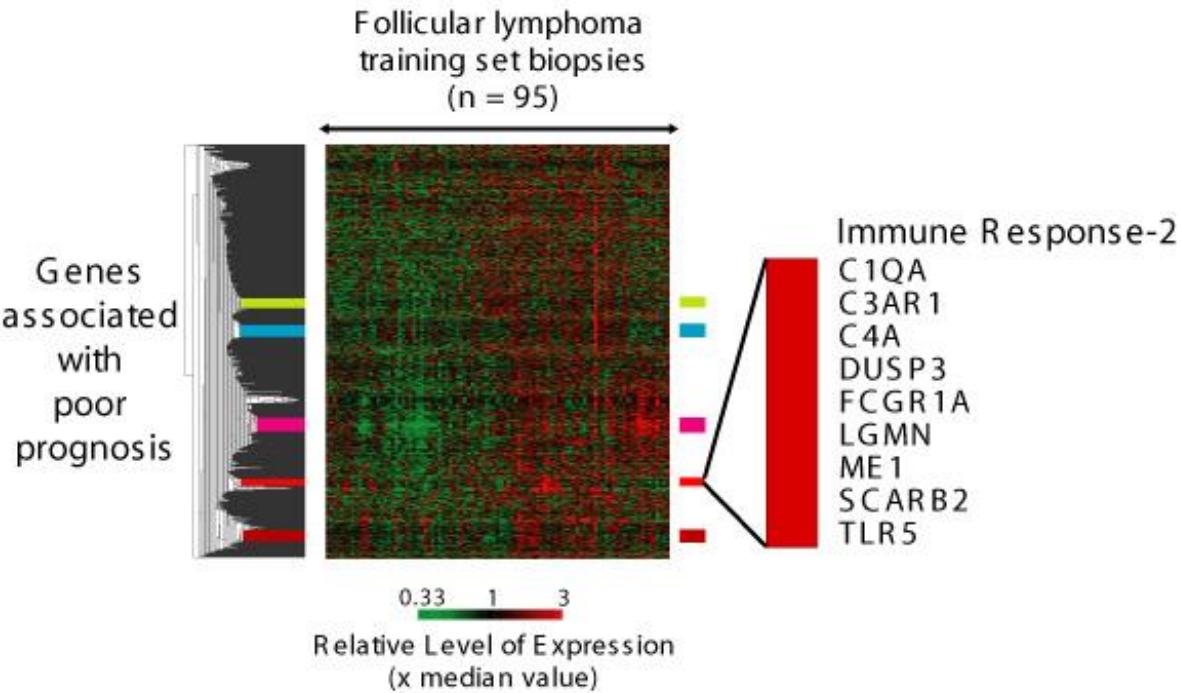
Hemoglobin <12 vs. < 12

# Identification of gene expression signatures associated with favorable prognosis



Mostly  
T cell genes?

# Identification of gene expression signatures associated with poor prognosis

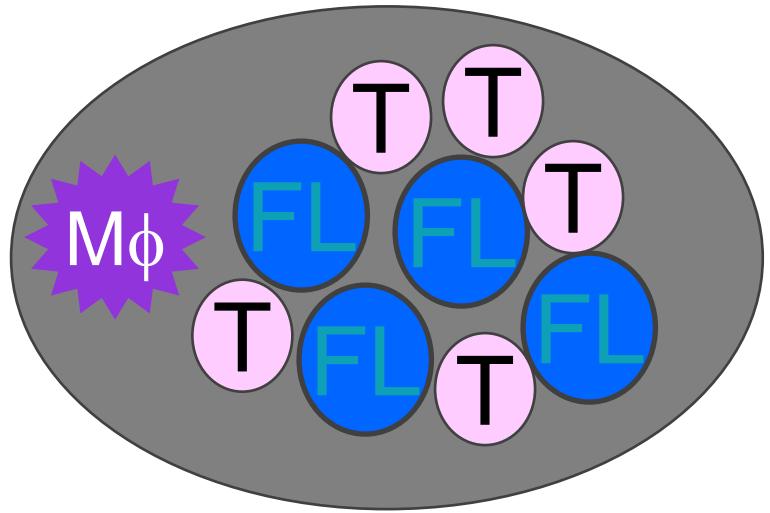


Mostly  
macrophage  
genes?

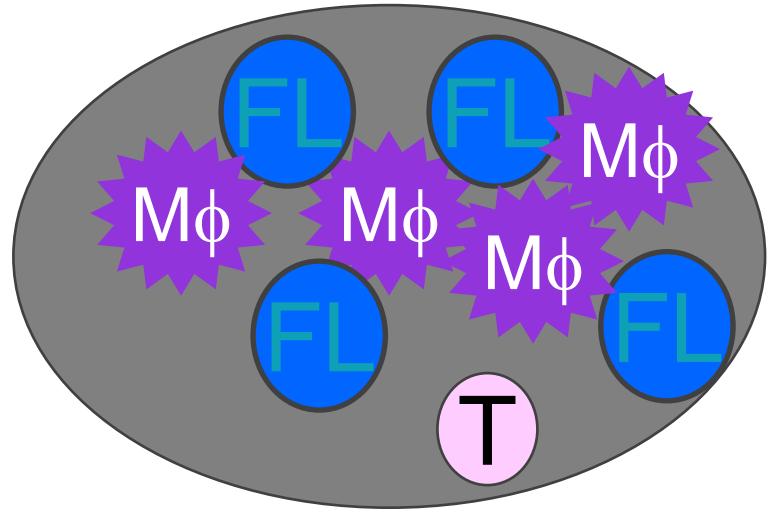




# Potential Influence of the Immune System on Survival In Follicular Lymphoma

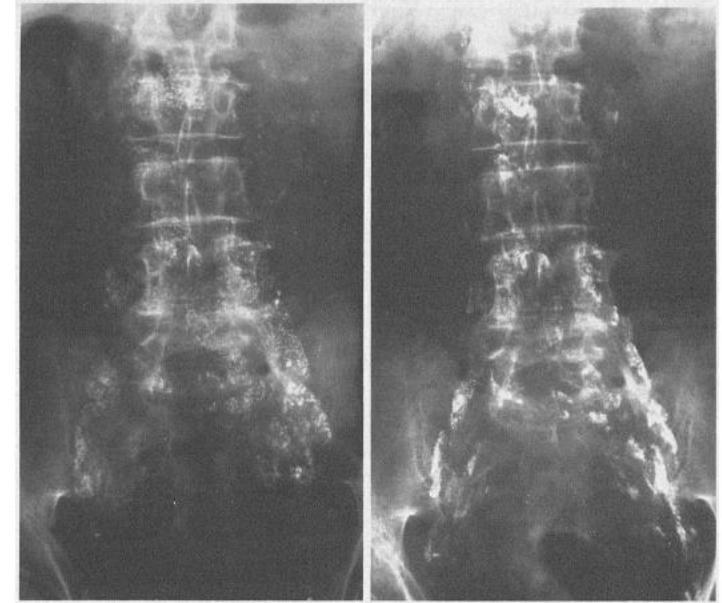
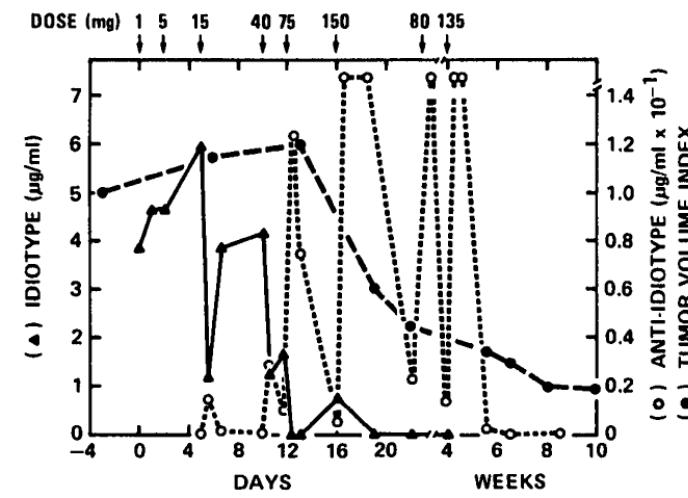
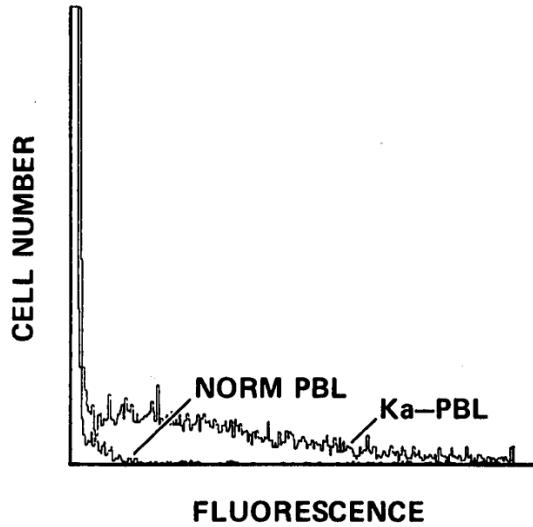


**Patient 1:**  
**Longer survival**



**Patient 2:**  
**Shorter survival**

# 4D6 Antibody in a 67 year old with FL, treated with observation, interferon, CVP, CVP +Bleomycin then....



Miller, Maloney, Warnke, Levy NEJM 1982; 306 (9): 517



# Monoclonal Antibody 1F5 (Anti-CD20) Serotherapy of Human B Cell Lymphomas

By Oliver W. Press, Frederick Appelbaum, Jeffrey A. Ledbetter, Paul J. Martin, Joyce Zarling, Pamela Kidd, and E. Donnall Thomas

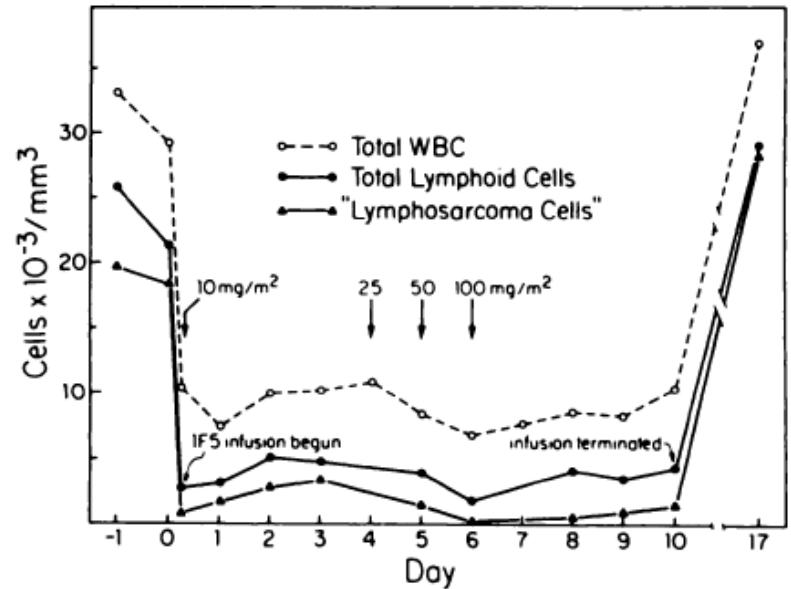


Fig 2. Depletion of circulating lymphoma cells in patient 3 during infusion of MoAb 1F5.

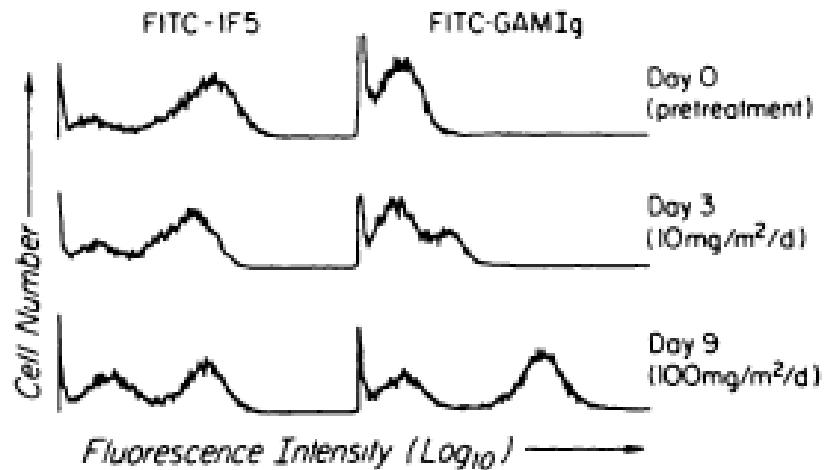
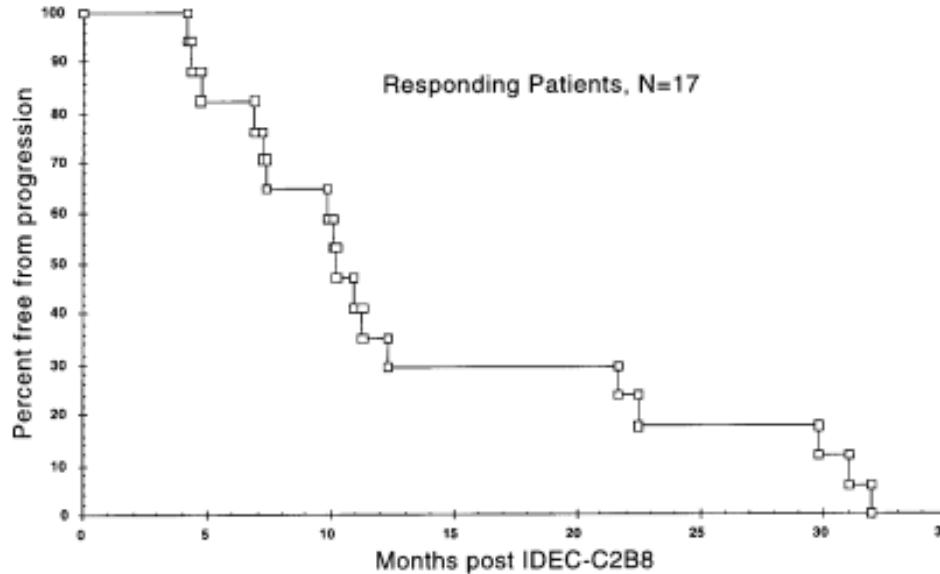


Fig 4. Penetration of MoAb 1F5 into bone marrow of patient 3 during serotherapy as assessed by flow cytometry of mononuclear cells from BM aspirates using FITC-GAM Ig (to detect cell-bound 1F5) and FITC-1F5 (to detect unbound Bp35 sites).

Press et al BLOOD 1987; 69 (2):584

# IDEC C2 B8 in Relapsed Refractory B-cell lymphoma



Phase I Trial n=17

Maloney et al BLOOD 1997; 90(6):2188

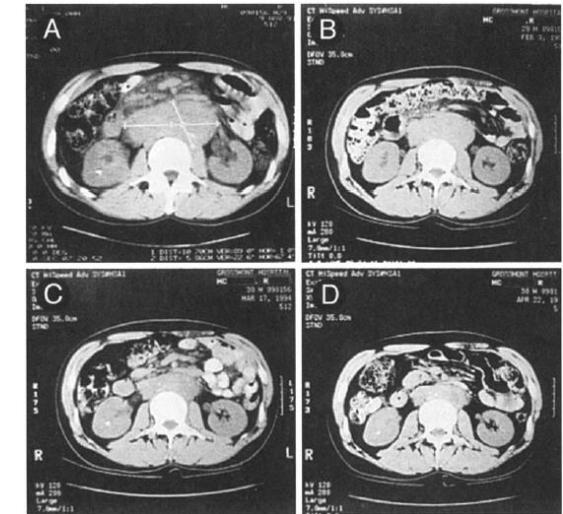
Table 5. Pharmacokinetic Parameter Summary: 375-mg/m<sup>2</sup> Dose

Patient No.	Model*	First Infusion			Fourth Infusion			Clinical Response
		T <sub>1/2</sub> (hours)	C <sub>max†</sub> (μg/mL)	Cl‡ (L/h)	T <sub>1/2</sub> (hours)	C <sub>max†</sub> (μg/mL)	Cl‡ (L/h)	
014	1	35.4	413.7	0.0196	106.0	663.9	0.0045	PD
016§	1	11.1	118.9	0.2820	26.4	131.3	0.1188	PD
017	1	53.1	230.9	0.0441	97.5	504.8	0.0114	PR
Mean		33.2	254.5	0.1152	76.6	433.3	0.0449	
SD		21.1	148.8	0.1449	43.7	273.4	0.0641	

Table 6. Dose-Response Relationship (N = 18)

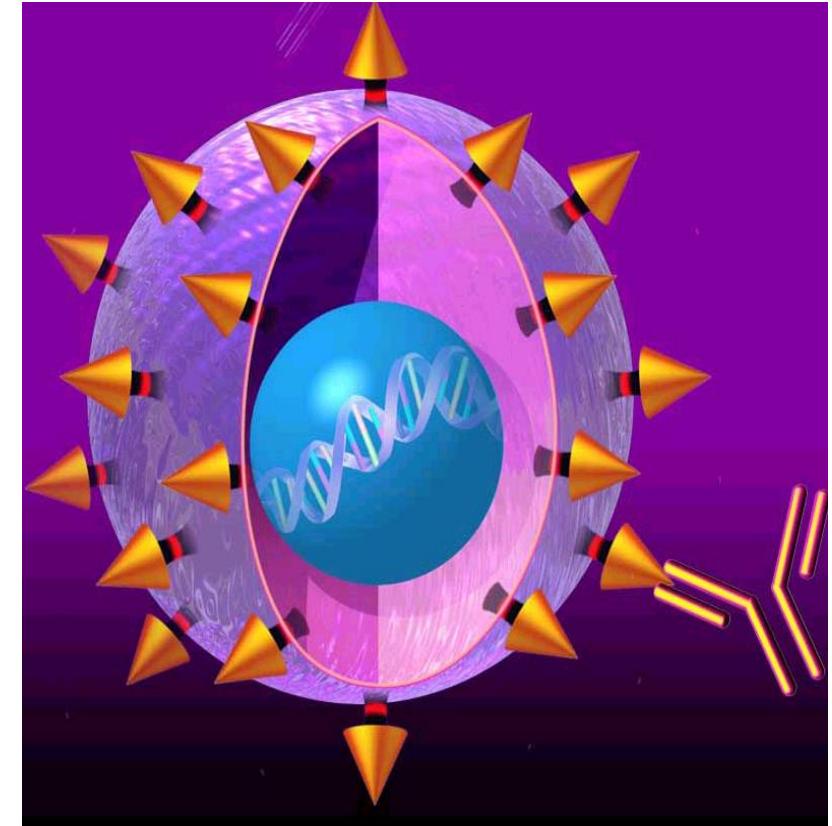
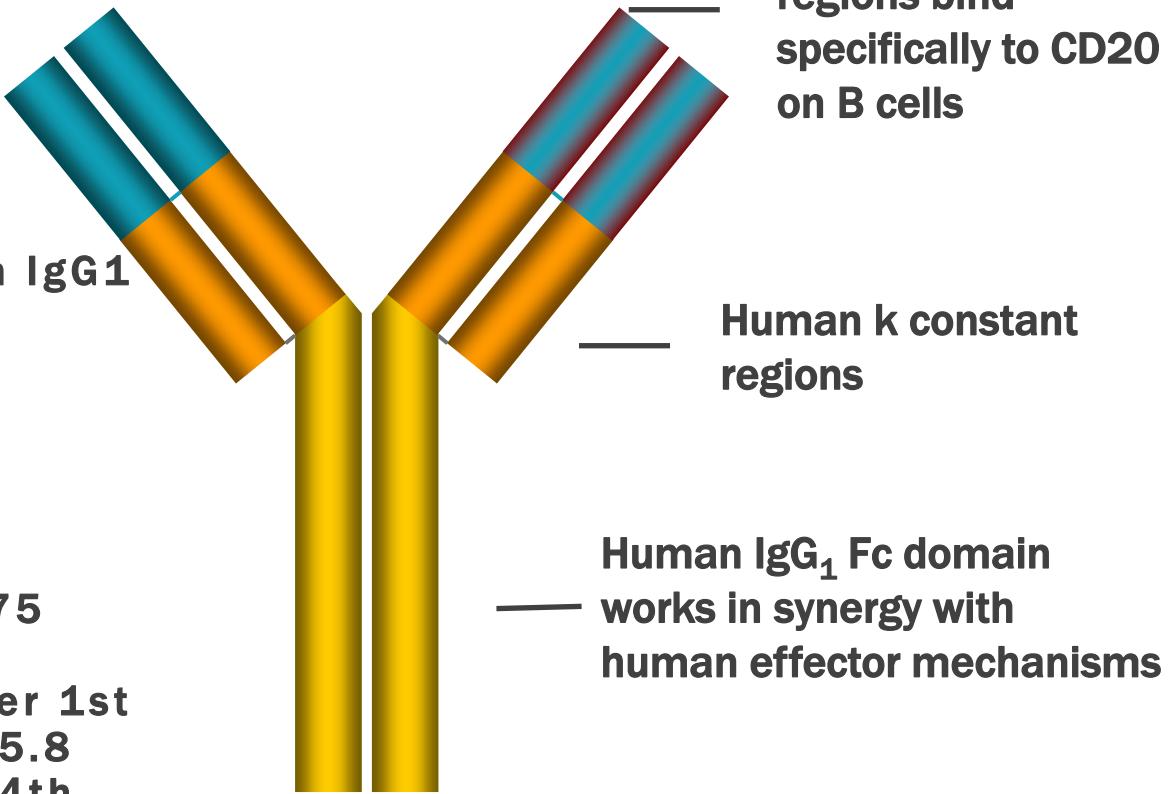
Response	Dose Group (mg/m <sup>2</sup> )		
	125	250	375
CR	0	0	0
PR	1	2	3
SD	1	2	3
PD	1	2	3
OR	1/3 (33%)	2/6 (33%)	3/9 (33%)

Phase II Trial n=21



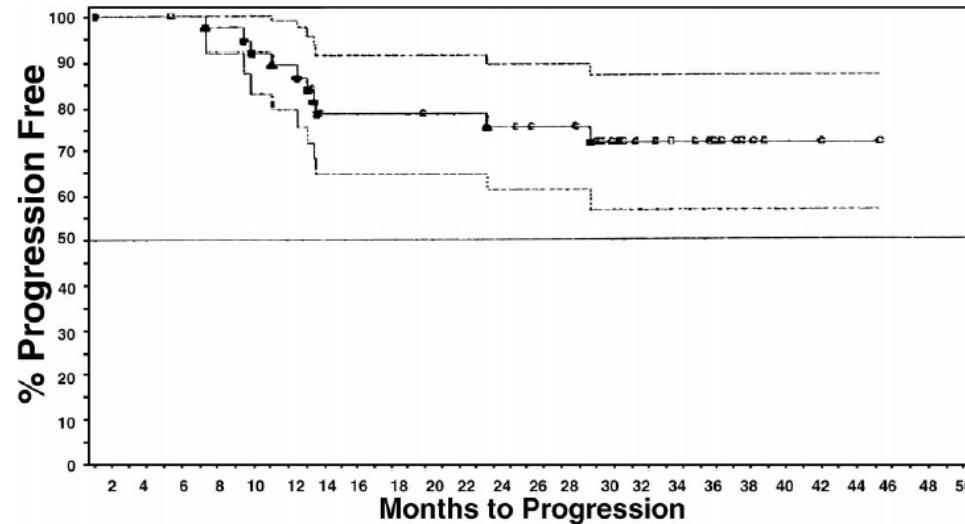
# IDEC C2B8, rituximab

- Murine/human IgG1 K monoclonal
- Binds to CD20 antigen
- Half-life (at 375 mg/m<sup>2</sup>)  
~76.3 hours after 1st infusion and 205.8 hours after the 4th infusion
- Mechanism of action: CDC, ADCC, apoptosis

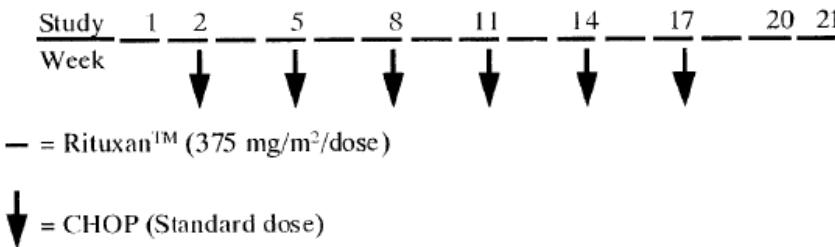


# Rituximab with chemotherapy in FL

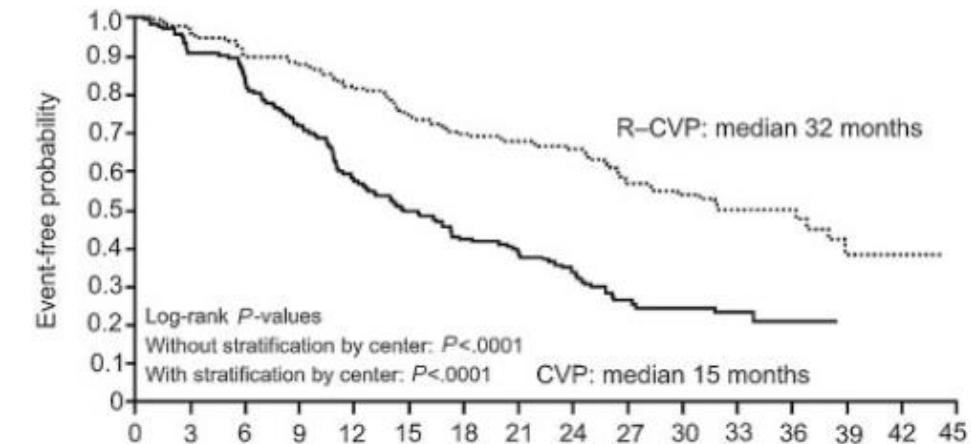
Czuczman et al JCO 1999



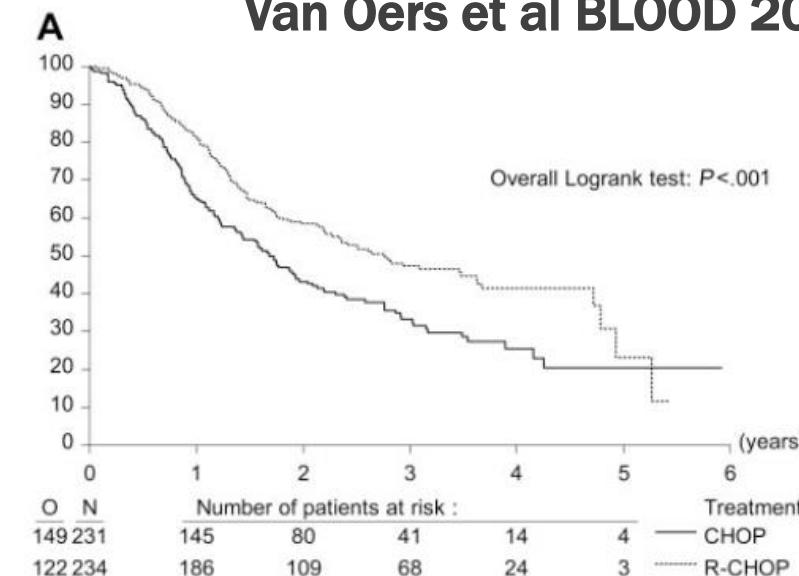
n=41, 31 previously untreated  
Prednisone at standard dose of 100/m<sup>2</sup>



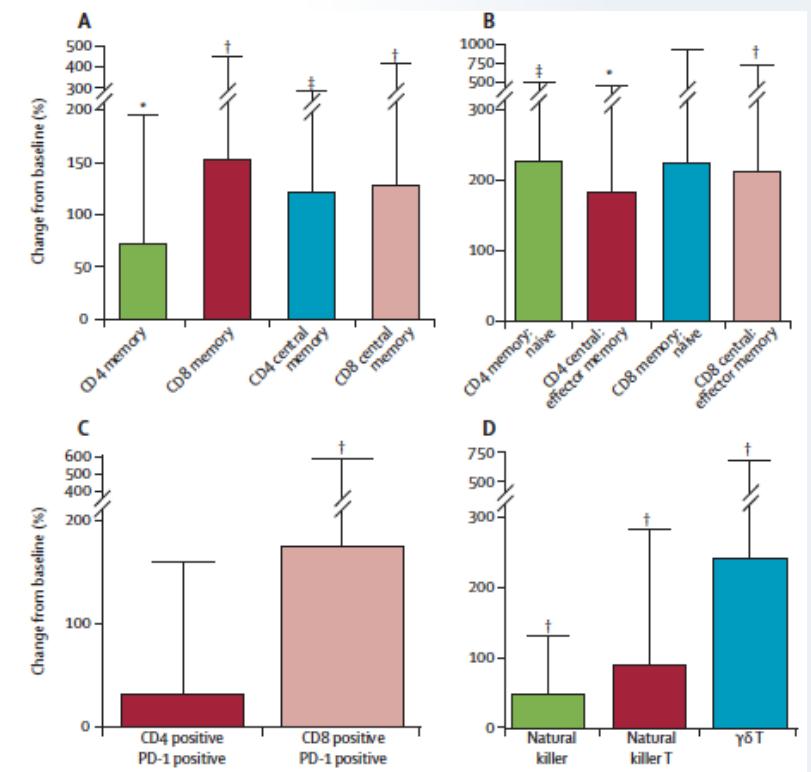
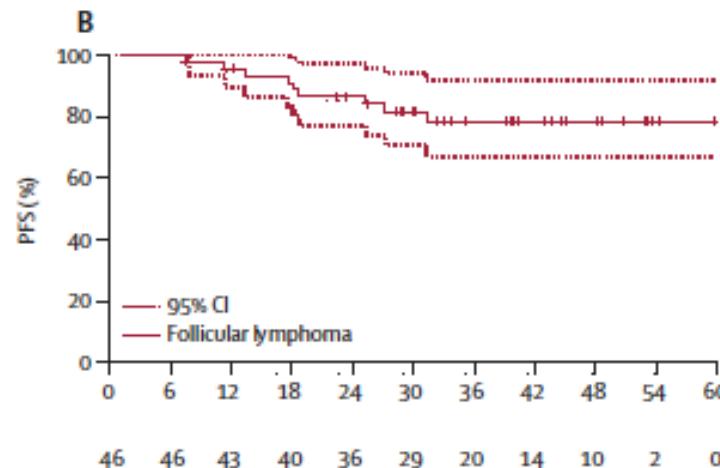
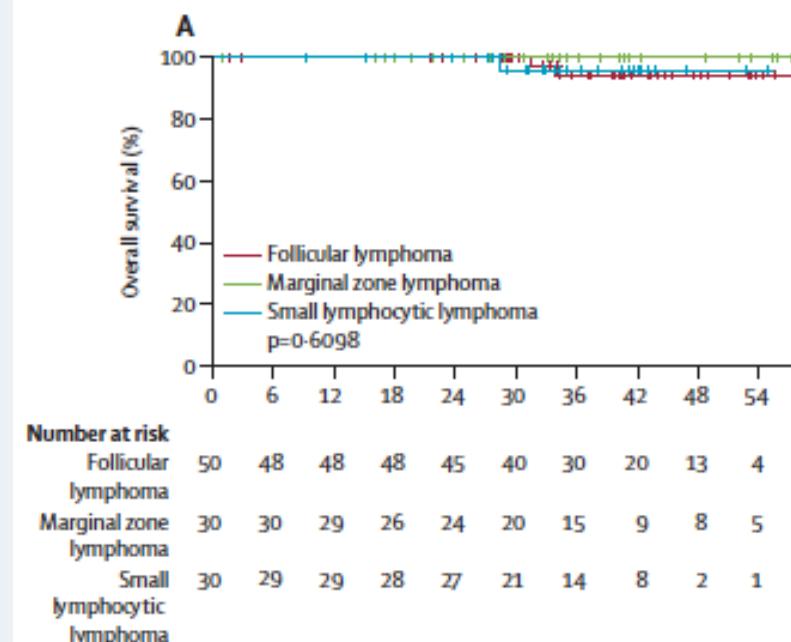
Marcus et al BLOOD 2005



Van Oers et al BLOOD 2006



# "Chemotherapy free" approach: R<sup>2</sup> in FL



Fowler et al Lancet Oncology 2014; 15:1311

# Yttrium-90-labeled Anti-CD20 Monoclonal Antibody Therapy of Recurrent B-Cell Lymphoma<sup>1</sup>

Susan J. Knox,<sup>2</sup> Michael L. Goris, Kirk Trisler, Robert Negrin, Thomas Davis, Tina-Marie Liles, Antonio Grillo-López, Paul Chinn, Chet Varns, Shou-Cheng Ning, Sherry Fowler, Nimisha Deb, Mark Becker, Carol Marquez, and Ronald Levy

Departments of Radiation Oncology [S. J. K., K. T., S-C. N., S. F., N. D., M. B., C. M.], Diagnostic Radiology, Division of Nuclear Medicine [M. L. G.], Medicine, Division of Bone Marrow Transplantation [R. N.], and Internal Medicine, Division of Medical Oncology [T. D., T-M. L., R. L.], Stanford University School of Medicine, Stanford, California 94305, and IDEC Pharmaceuticals Corporation, San Diego, California 92121 [A. G-L., P. C., C. V.]

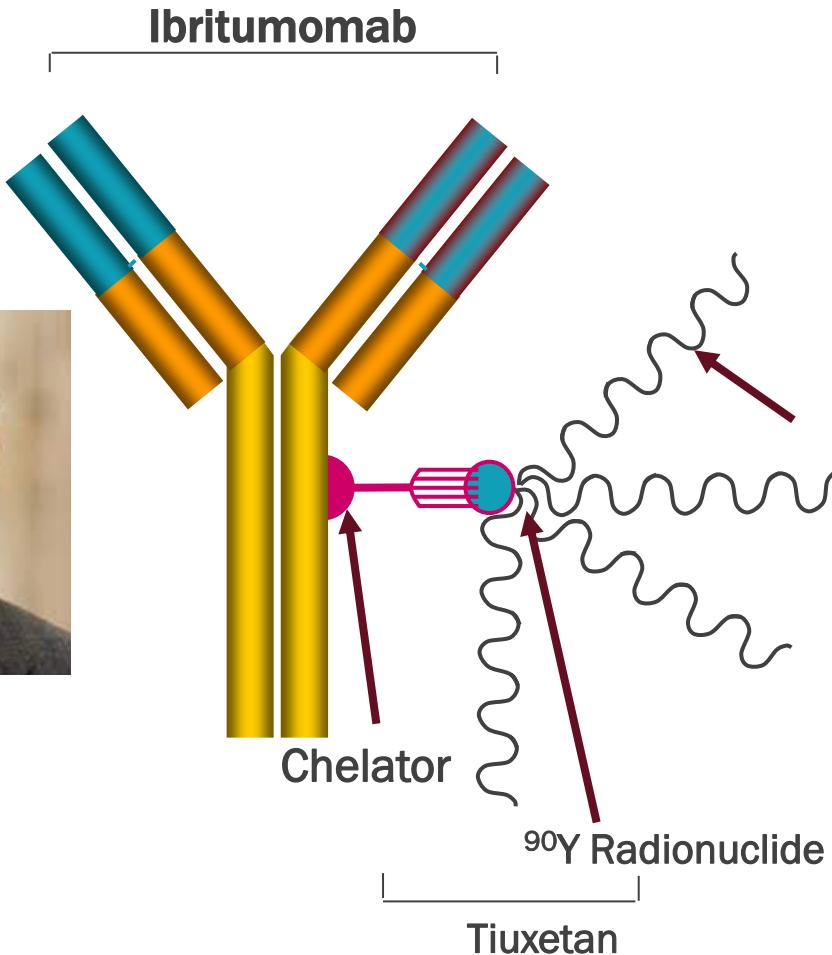
lymphoma. Doses of  $\leq 40$  mCi  $^{90}\text{Y}$ -anti-CD20 mAb were not myeloablative.

## INTRODUCTION

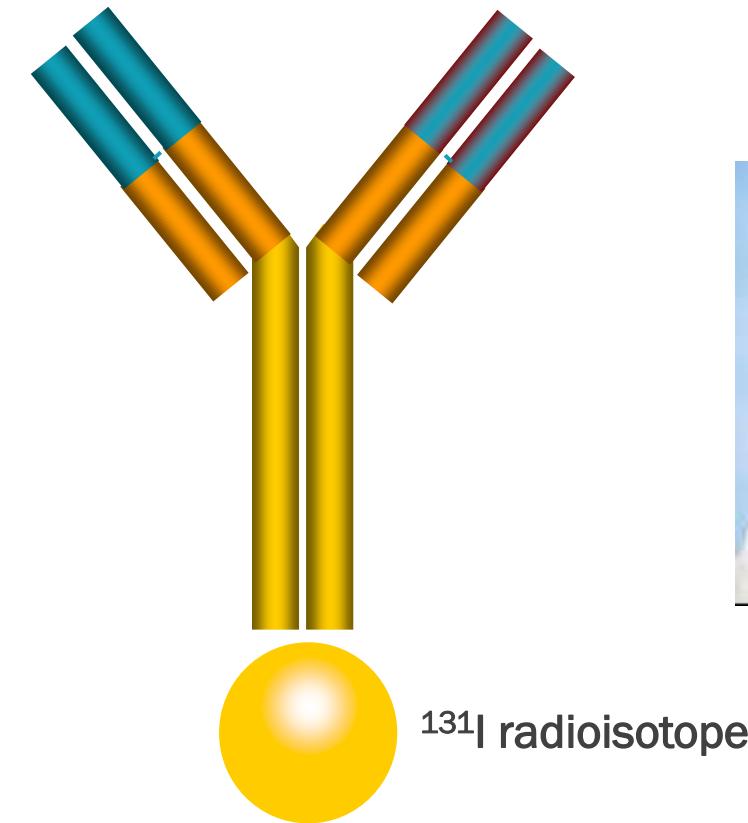
Most patients with recurrent B-cell lymphoma are generally considered to be incurable with standard chemotherapy (1), and new therapies are needed for this disease. Encouraging results have been obtained in clinical studies using unlabeled anti-idiotype and *pan-B* mAbs<sup>3</sup> for the treatment of patients with recurrent B-cell lymphoma (2–8). Although clinical responses have been observed using unlabeled mAb (2–8), they have been limited by a number of factors (9), including: (a) heterogeneity of antigen expression on tumor cells, (b) inacces-

# Radioimmunotherapy (RIT) in the Treatment of Follicular Lymphoma

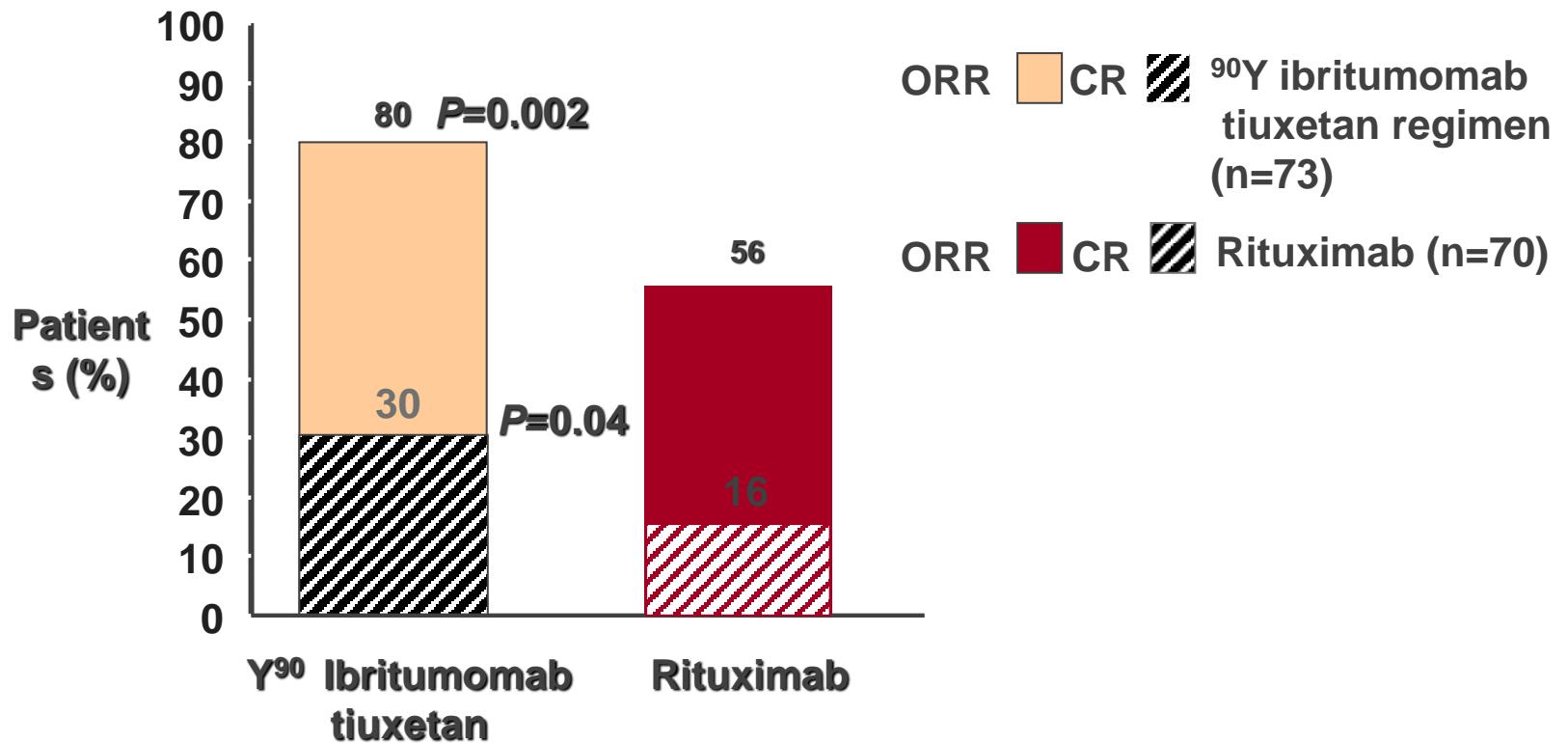
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**Tositumomab**



# Randomized Trial (106-04) of Ibritumomab Tiuxetan vs Rituximab: Response Data

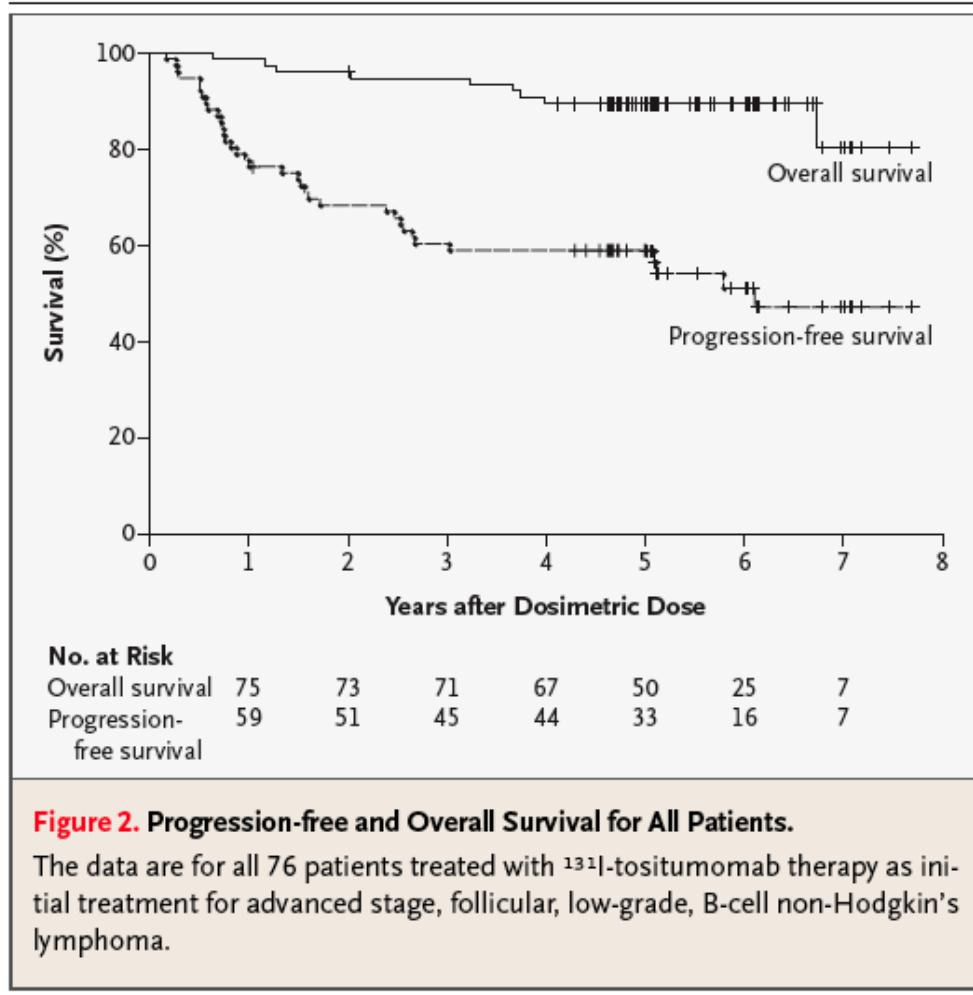




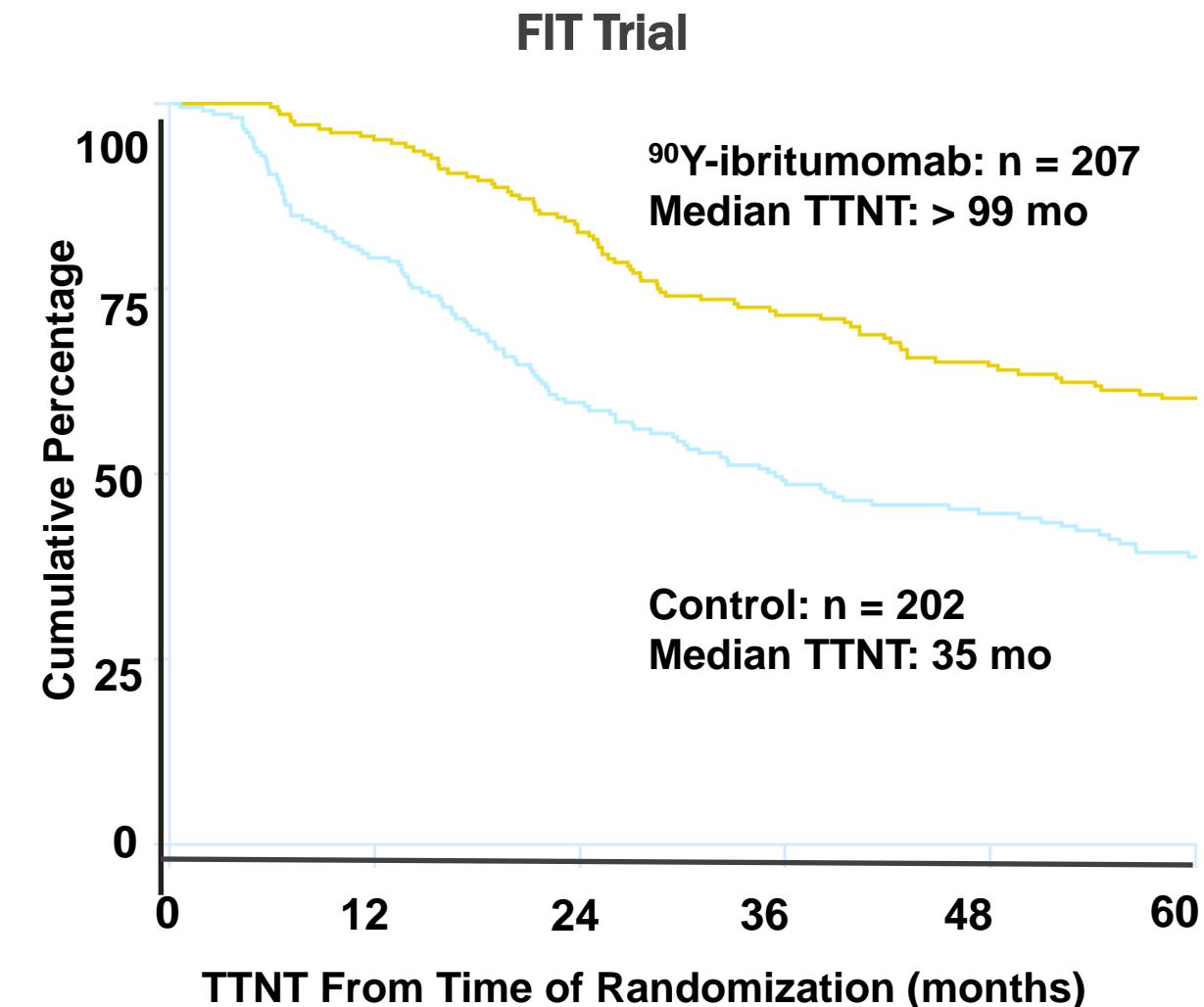
# RIT: As Front Line Treatment and as Consolidation



Kaminski et al NEJM 2005; 352:441

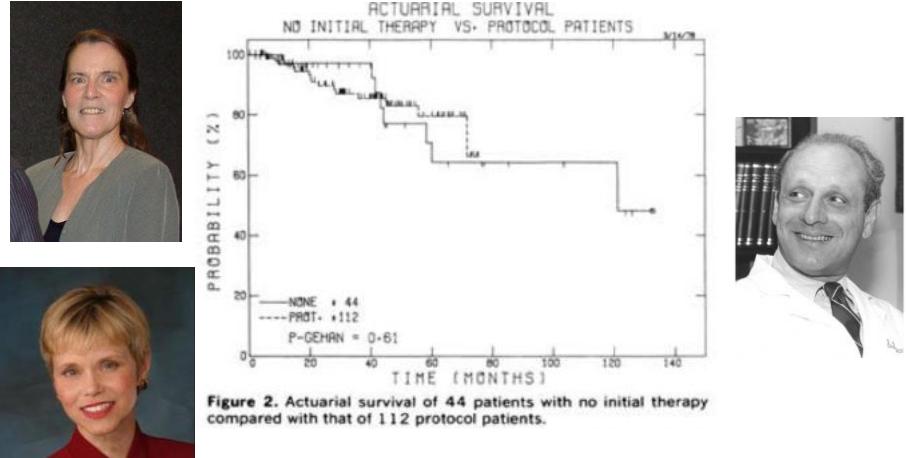


Morschhauser et al. JCO 2008;26:5156.

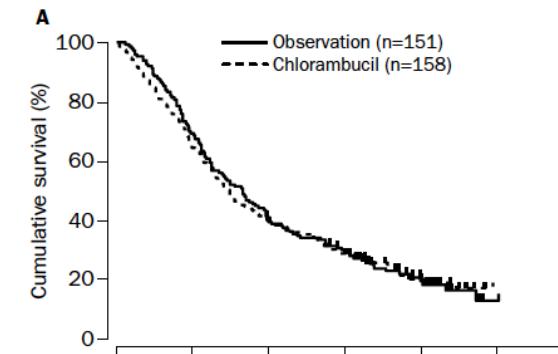


# Early Studies in FL: The Watch and Wait Concept

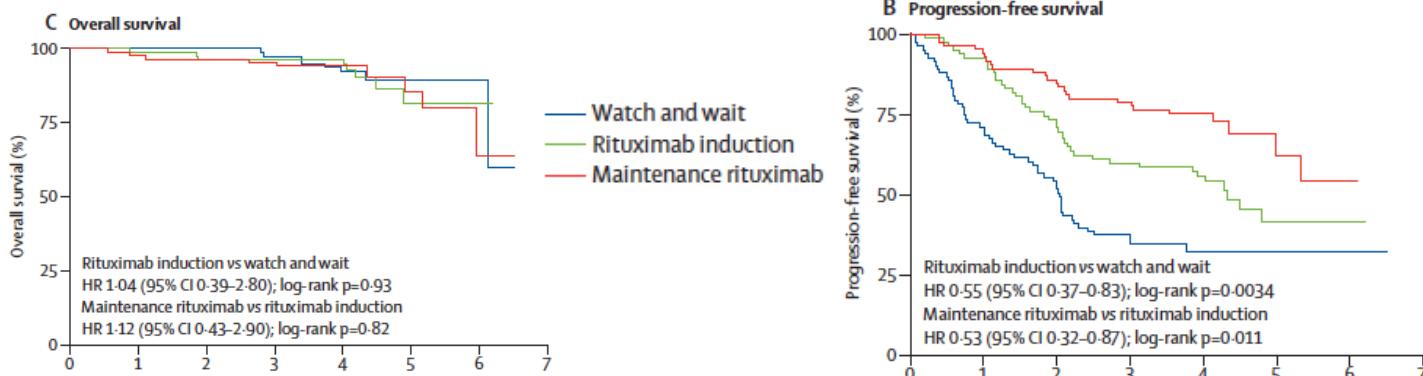
Portlock and Rosenberg Ann Int Med 1979



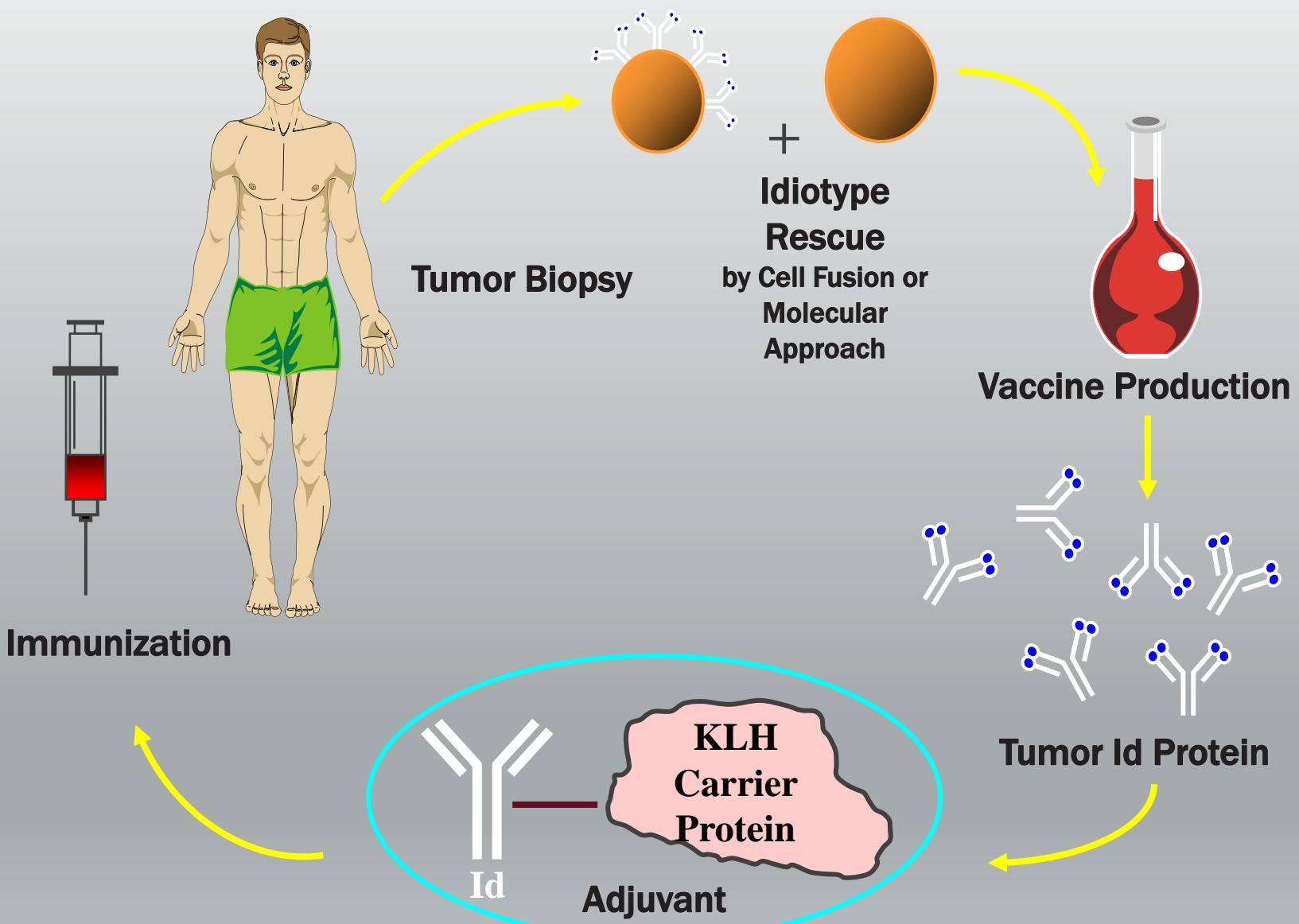
Ardesina et al Lancet 2003



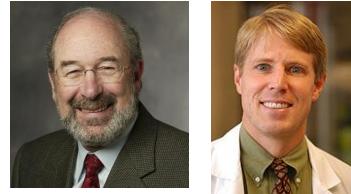
Ardesina et al Lancet Oncology 2014



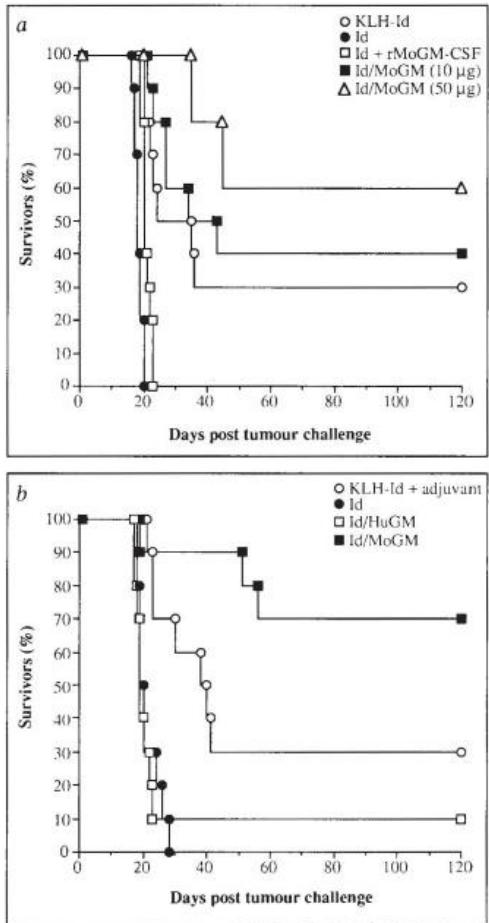
# Preparation of Idiotype Vaccine



# Anti Id Vaccines

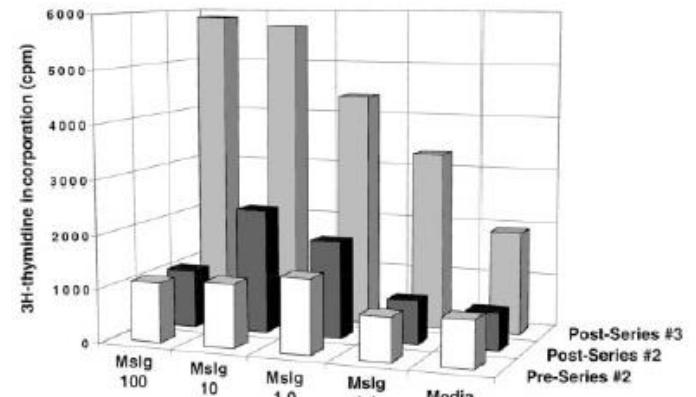
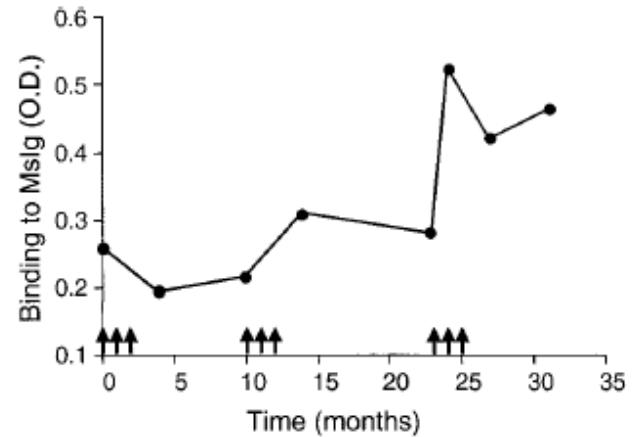


## Murine Experiments



Tao and Levy Nature 1993; 36 2(6422):755

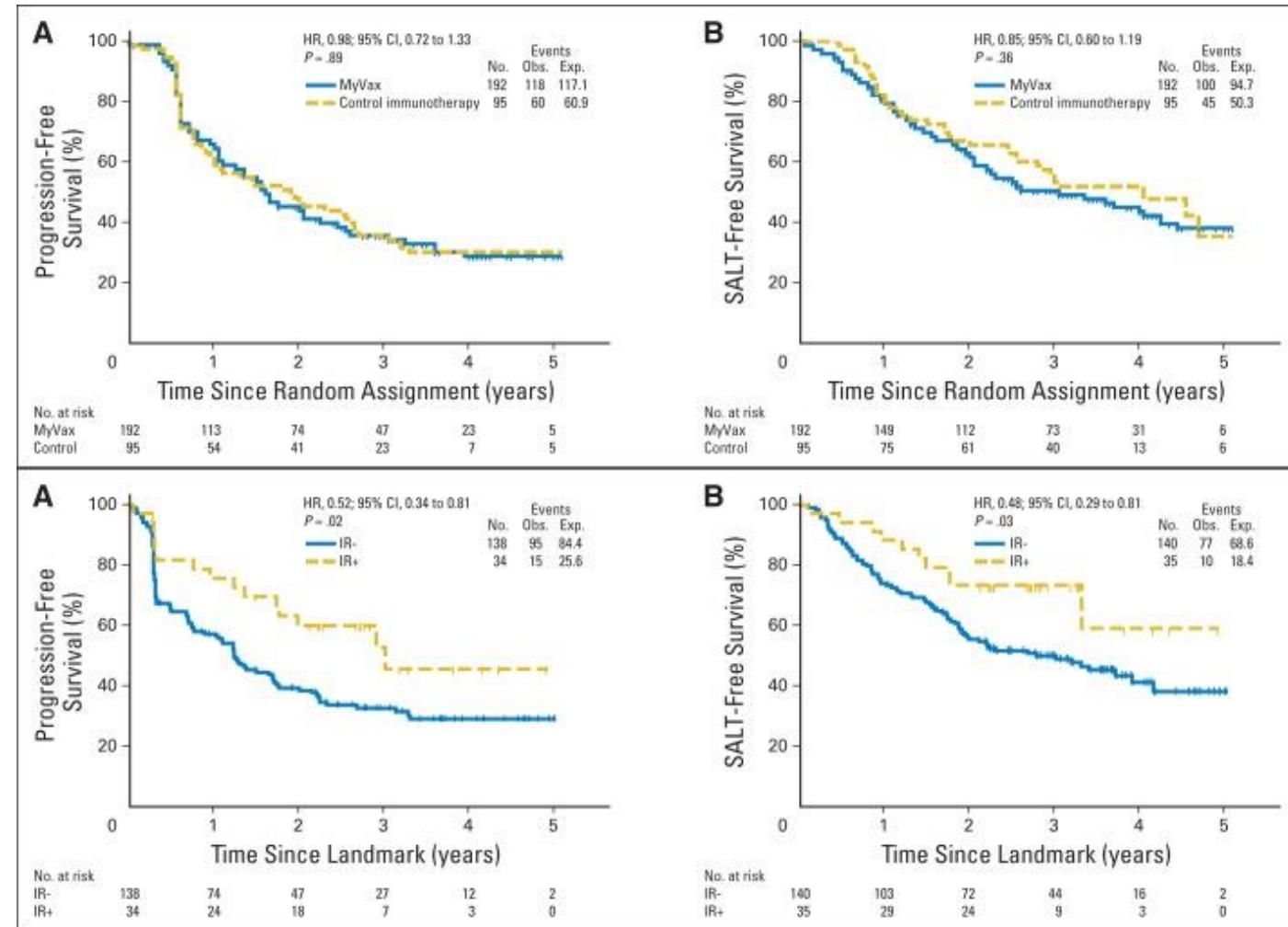
## Phase 1 Trial (n=12)



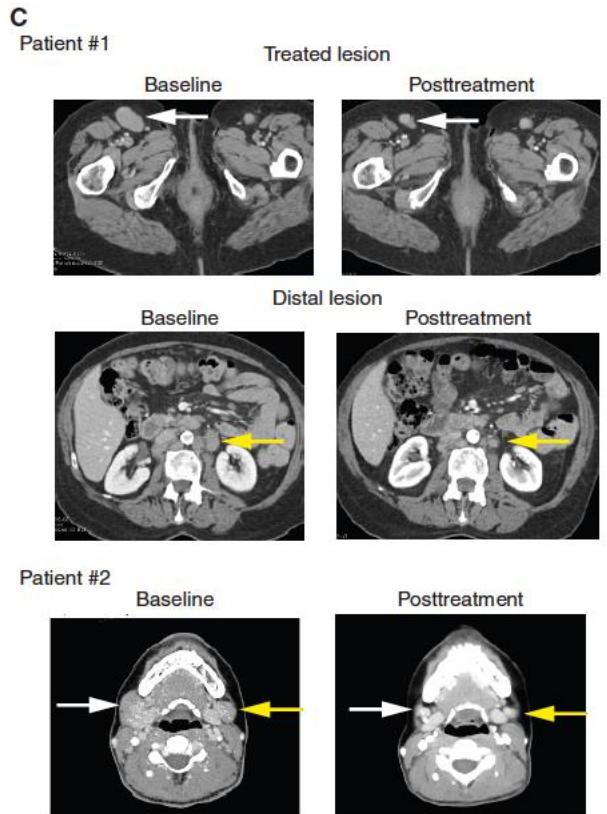
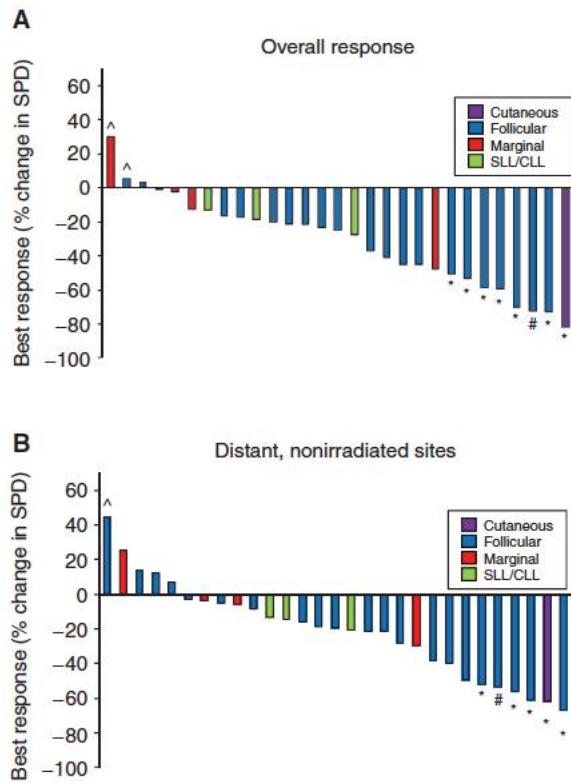
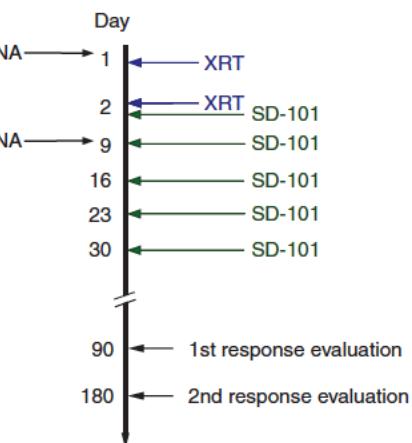
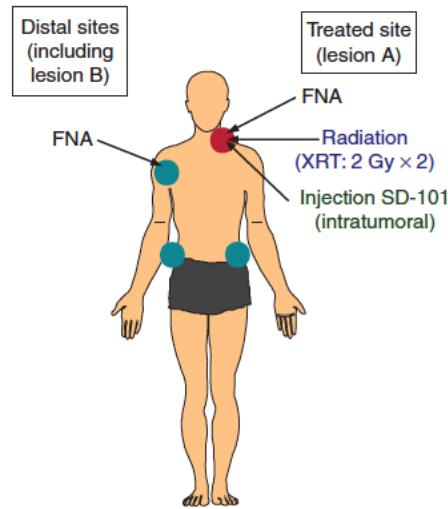
Timmerman et al Cancer Res 2002; 62(20):5845

# Randomized Trial of anti-Id vs control after CVP x 8 in FL

- n=687
- CRs (44% n=287) randomized
- No difference in PFS or next lymphoma treatment
- Those with anti-Id response did better

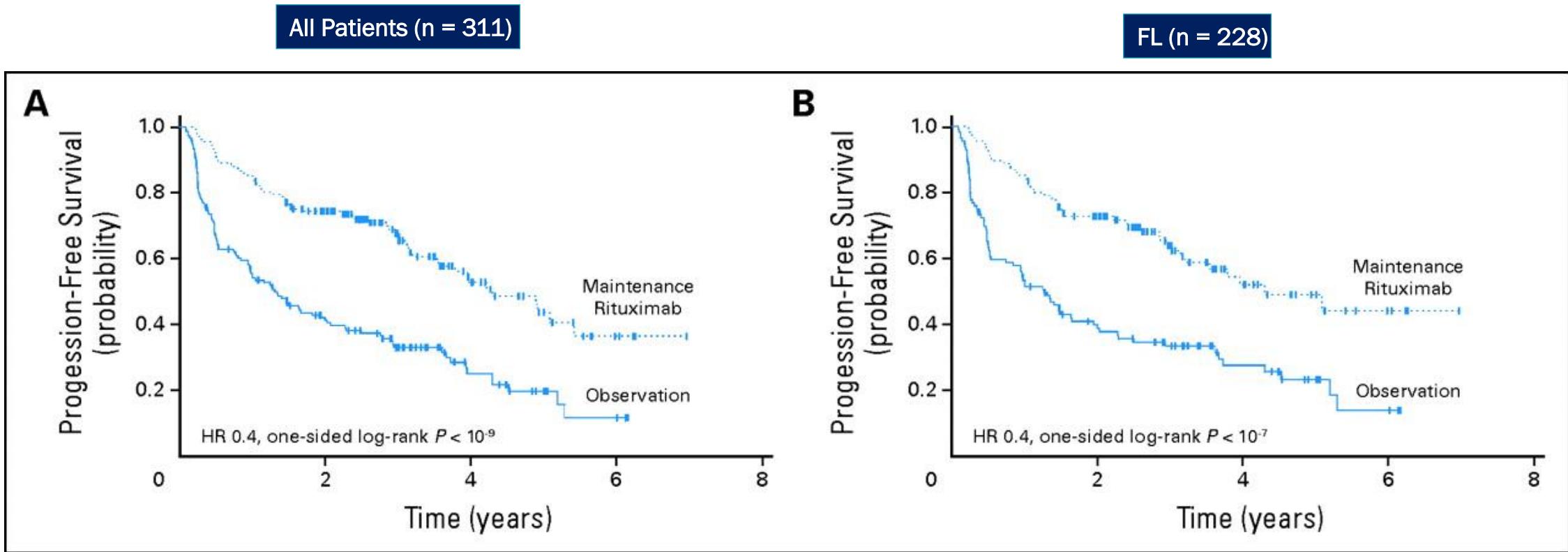


# In Situ vaccination in low grade lymphoma



Frank et al Cancer Discovery 2018; 8(10): 1258

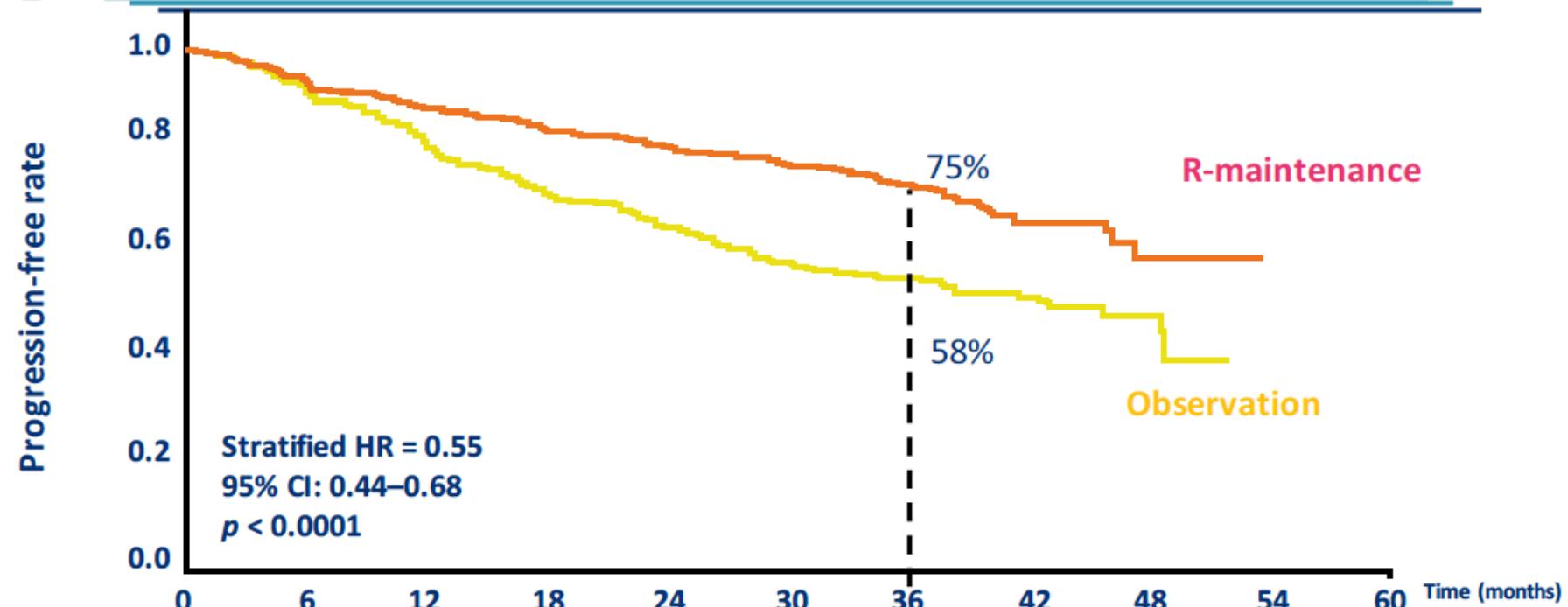
# Maintenance Rituximab Improves PFS in Indolent and FL Patients Following CVP Chemotherapy (E 1496)



Hochster H, et al. *J Clin Oncol.* 2009;27:1607-1614.



## PRIMA : Primary endpoint (PFS): 3 years



Patients at risk

PRIMA 10 YEARS

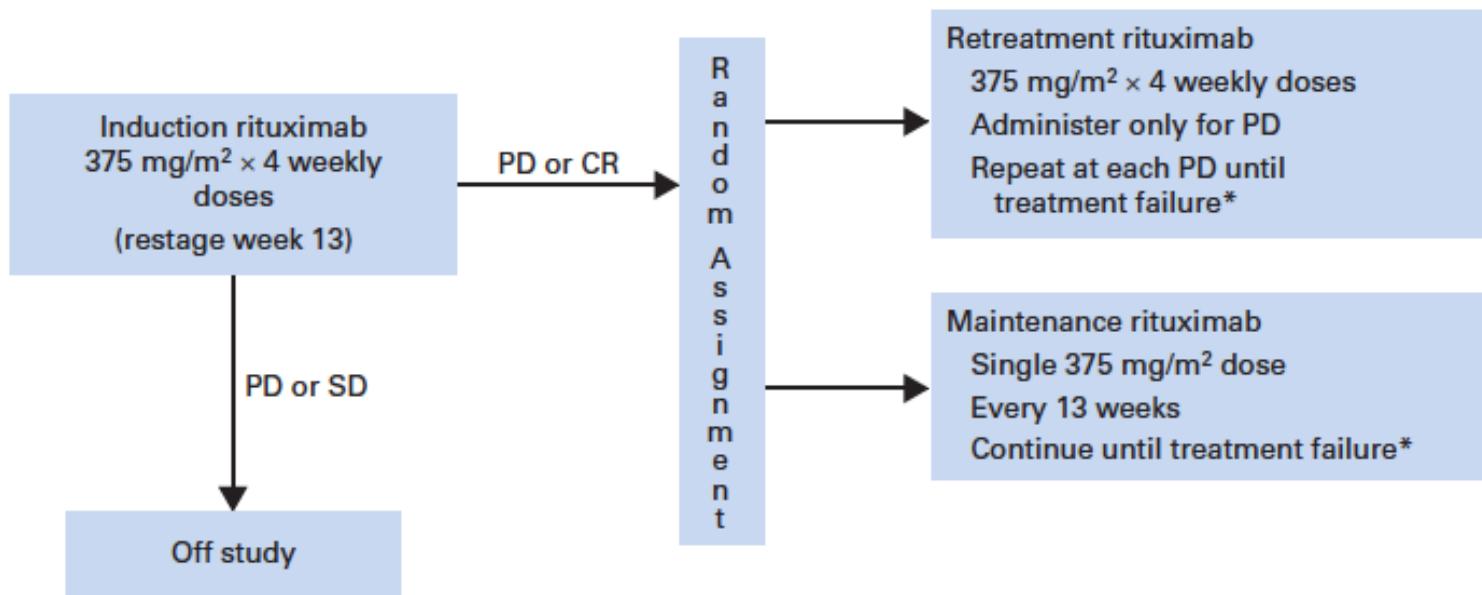
59th ASH Annual Meeting, Atlanta, GA, December 9-12, 2017

Oral Session - Abstract #486

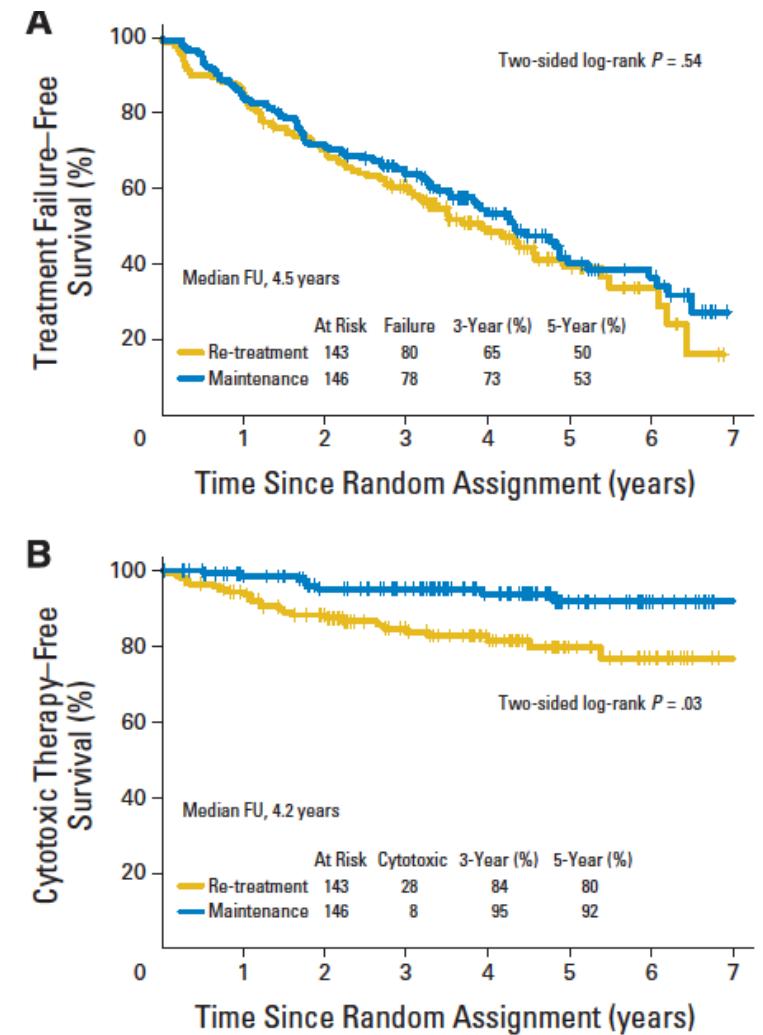
6



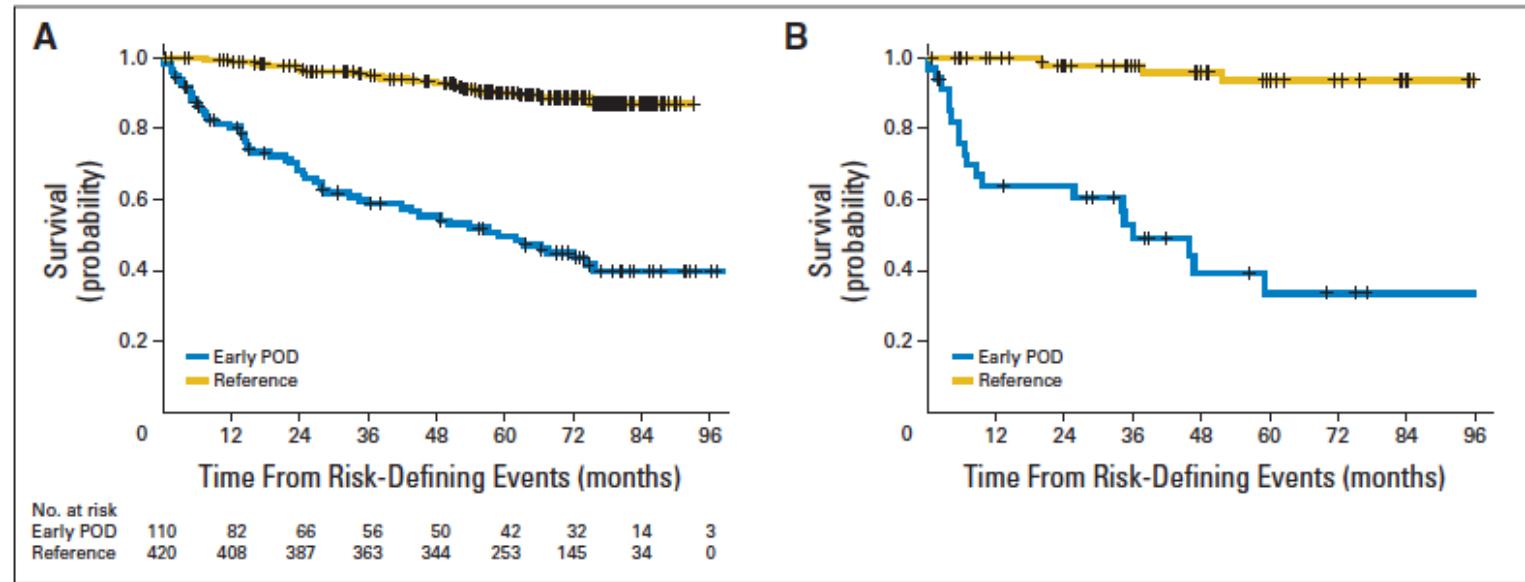
# RESORT Trial: No advantage in PFS in low tumor burden FL



Kahl et al JCO 2014; 32(28): 3096



# POD 24 in FL



A) National LymphoCare data n=588

B) Validation set Mayo/Iowa SPORCE n=147

Casulo et al JCO 2015; 33 (23):2516



# Mosunetuzumab in FL

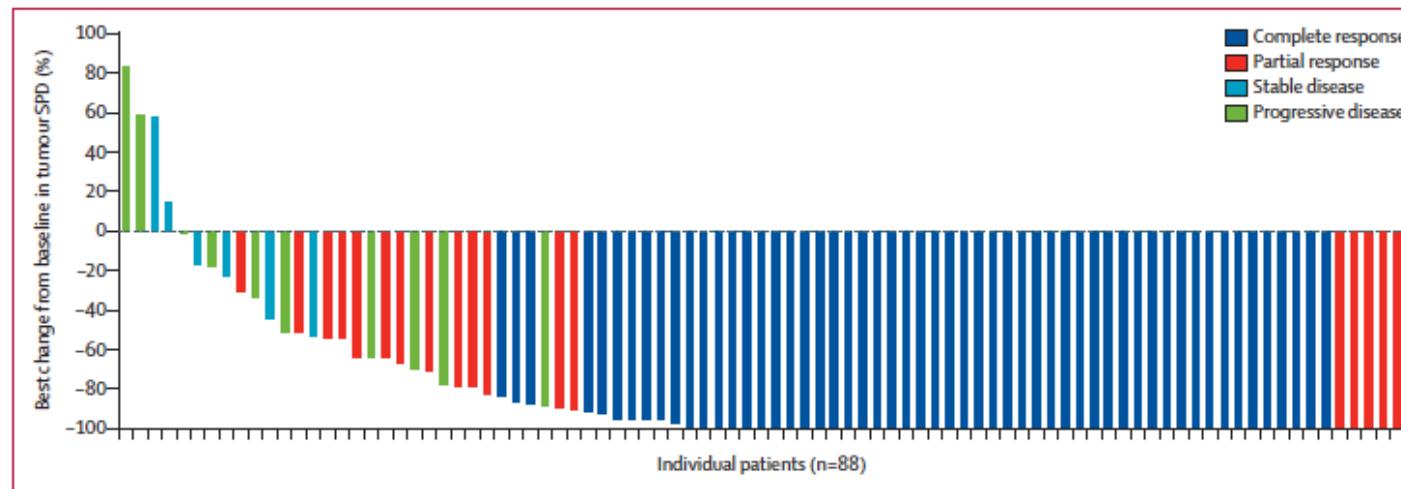
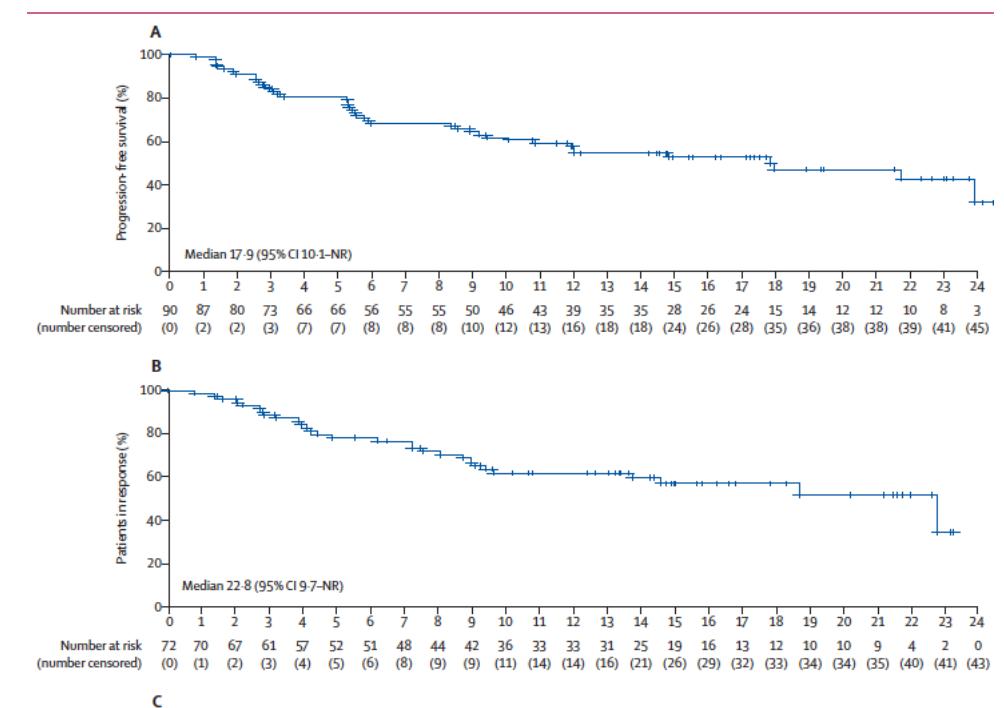


Figure 2: Waterfall plot of best percentage change in SPD  
SPD= sum of the products of diameters.

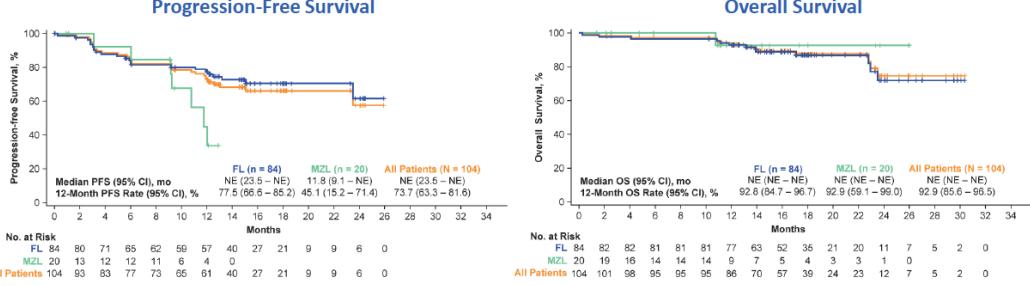


Budde, et al. Lancet Oncol 2022; 23 (8 ):1055



# CAR t in FL

## Progression-Free Survival and Overall Survival

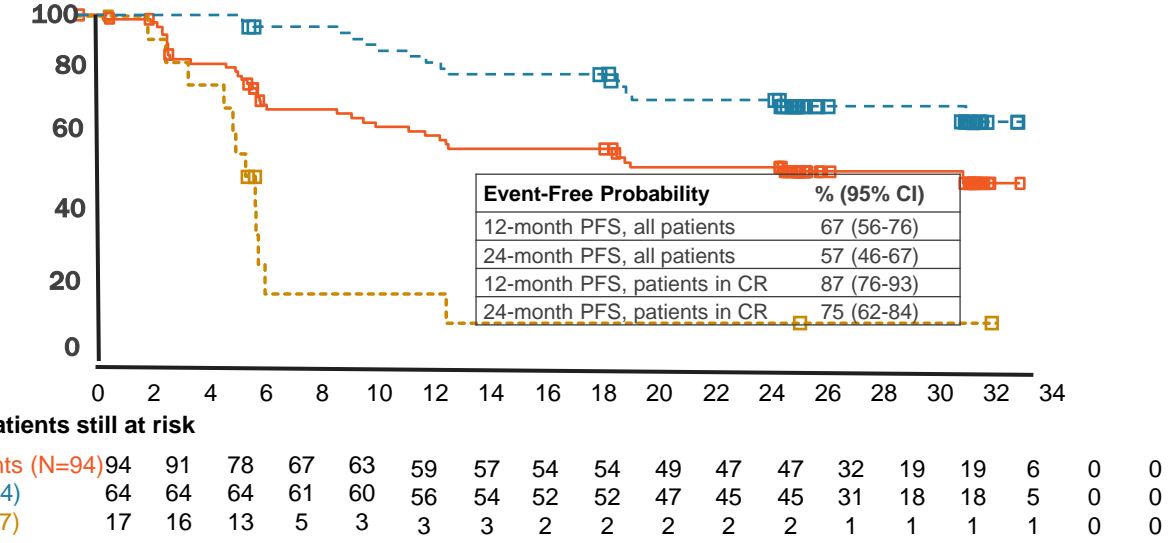


- With a median follow-up of 17.5 months, median PFS and median OS were not reached
  - The 12-month PFS rate was 73.7% (95% CI, 63.3 – 81.6) for all patients
  - The 12-month OS rate was 92.9% (95% CI, 85.6 – 96.5) for all patients

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

9 Jacobson et al ASH 2020 Abstract 700

**Kaplan-Meier medians**  
**All patients:** NE mo, 95% CI [18-NE]  
**CR:** NE mo, 95% CI [NE-NE]  
**PR:** 6 mo, 95% CI [5-6]



## ZUMA 5

Jacobson et al Lancet Oncol 2022; 23(1):91

## ELARA

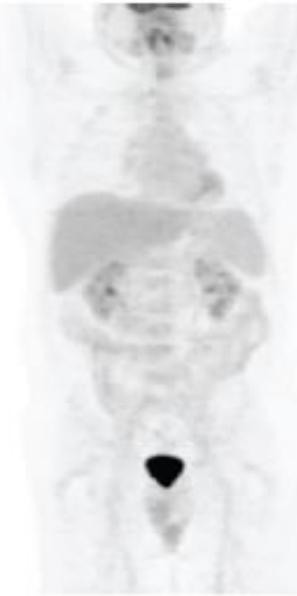
Fowler et al Nature Medicine 2022; 28 (2):325



# Pre-Diagnostic BCL2 and CREBBP-KAT mutations in FL

H

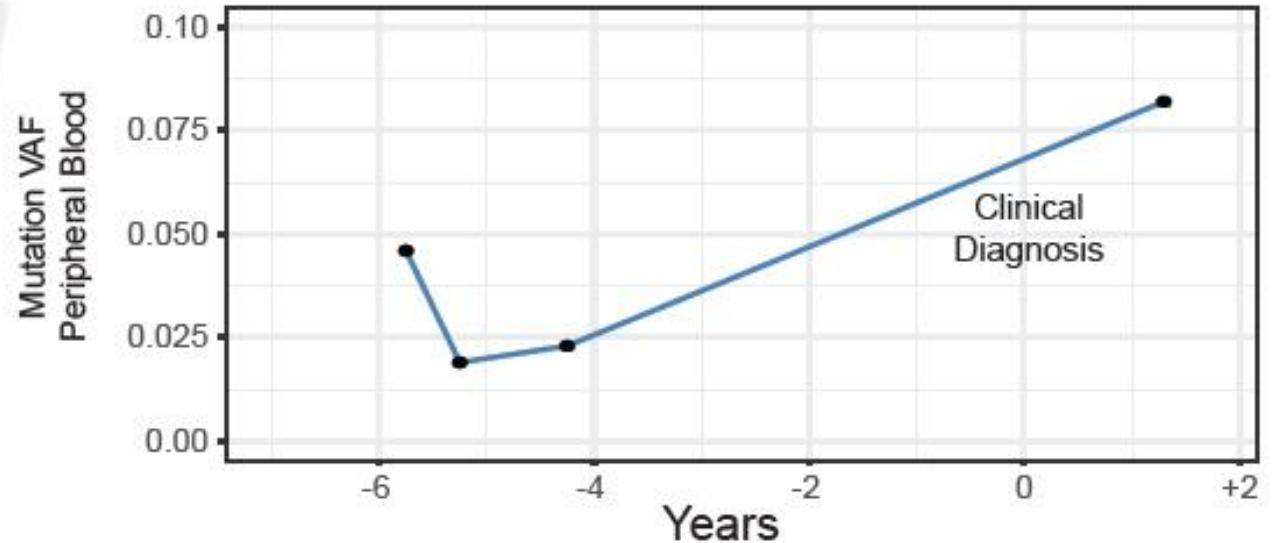
ISFN - 8 Years Prior  
Screening PET/CT



FL - Diagnosis  
Staging PET/CT

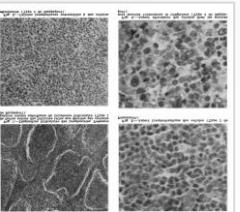


*CREBBP R1446C*



J. G. Schroers-Martin, J. Soo, G. Brisou, F. Scherer, D. M. Kurtz, B. J. Sworder, et al. *Cancer Discovery* 2023

## 1925-1938



- **Brill-Symmers Disease:** Brill et al JAMA 1925; Symmers Arch Pathol 1938

## 1979

- **Observation in FL:** Portlock et al Ann Int Med 1979



## 1980-1987

- **4D6 Ab :** Miller et al NEJM 1982
- **1F5 Ab:** Press et al Blood 1987



## 1993-2002



- **Vaccine:** Tao and Levy Nature 1993; Timmerman et al Cancer Res 2002
- **IDEA C2B8 (rituximab):** Maloney Blood 1997; Maloney JCO 1997
- **RIT:** Tositumomab: Kaminski et al NEJM 1993; Ibrutinomab tiuxetan: Witzig et al JCO 1999
- **R-CHOP:** Czuczman et al BLOOD 1997

## 2009-11



- **FLIPI 2:** Federico et al JCO 2009
- **R Maintenance:** Hochster, H et al JCO 2009 ; Salles et al Lancet 2011

## 2012-15

- **Observation:** Solal-Celigny JCO 2012
- **R vs W&W:** Ardesna et al Lancet Oncol 2014; Kahl et al RESORT JCO 2014
- **No advantage Id vaccine:** Levy et al JCO 2014
- **R<sup>2</sup>:** Fowler et al Lancet Oncology 2014
- **POD 24:** Casulo et al JCO 2015
- **M-7 FLIPI:** Pastore et al Lancet Oncology 2015



## 2003-06

- **Observation vs treatment:** Ardesna et al Lancet 2003
- **FLIPI 1:** Solal-Celigny et al BLOOD 2004
- **Molecular Features of FL:** Dave et al NEJM 2004
- **R-CVP vs CVP:** Marcus et al BLOOD 2005
- **R-CHOP vs CHOP:** vanOers et al BLOOD 2006



## 2021-23

- **CAR T:** ELARA Fowler et al Nature Medicine 2021; ZUMA 5 Jacobson et al Lancet Oncol 2022
- **Bi-Specifics :** Budde et al Lancet Oncol 2022
- **Founder Mutations in FL :** Schroers-Martin et al Cancer Discovery 2023